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- Modeling of inhalation anaesthesia
- Psychological impairment after cardiac surgery
- Lazaroids

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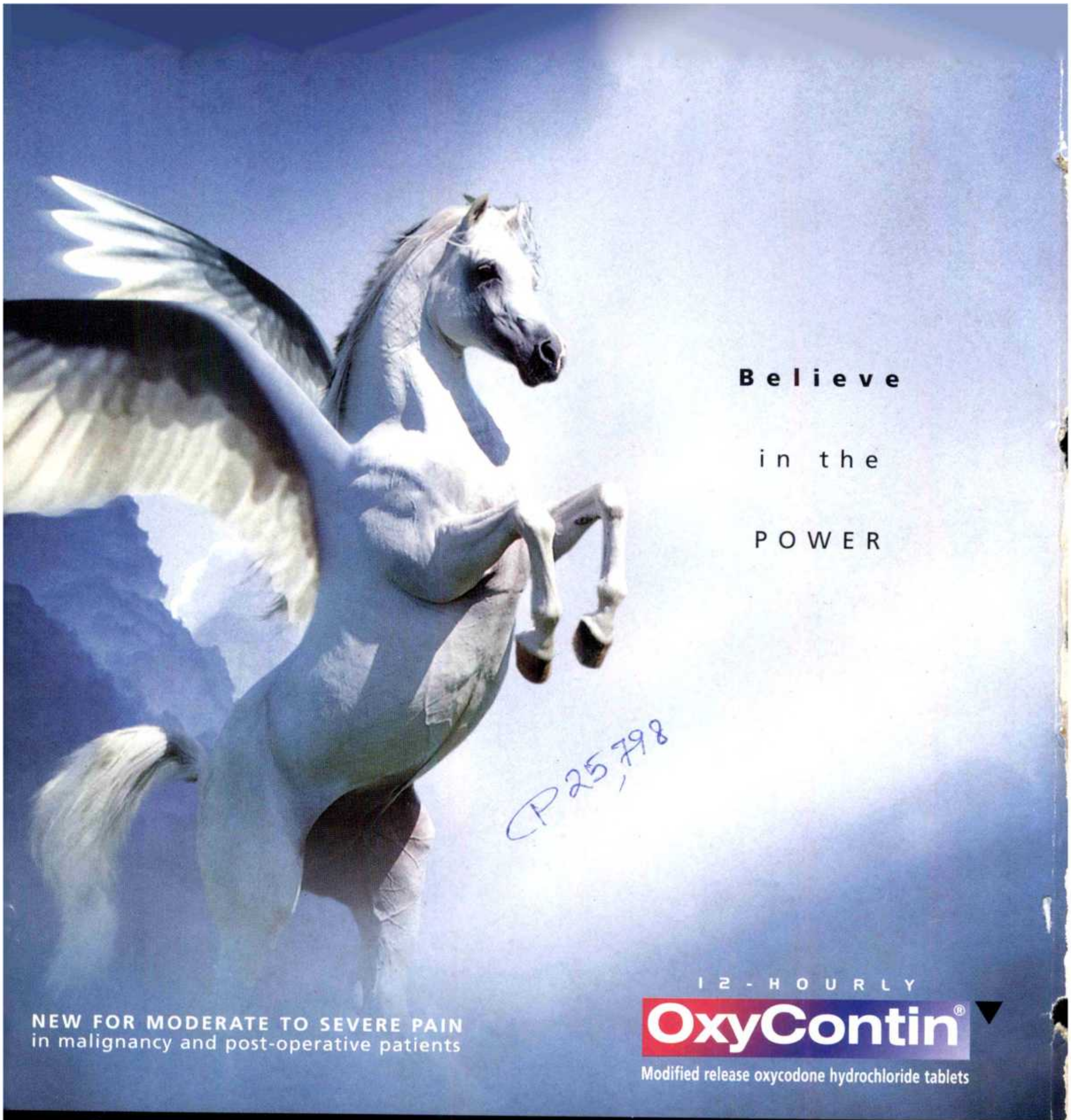
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Volume 86 Number 1 January 2001

EDITORIALS

1 I: Can we characterize the central nervous system actions of α_2-adrenergic agonists?
M. E. P. Jones and M. Maze

3 II: Publishing changes in 2001
G. Smith

CLINICAL INVESTIGATIONS

5 Sedative, analgesic, and cognitive effects of clonidine infusions in humans
J. E. Hall, T. D. Uhrich and T. J. Ebert

12 Model-based administration of inhalation anaesthesia. 1. Developing a system model
J. G. C. Lerou and L. H. D. J. Booij

29 Model-based administration of inhalation anaesthesia. 2. Exploring the system model
J. G. C. Lerou and L. H. D. J. Booij

38 Effects of sevoflurane and propofol on pulmonary shunt fraction during one-lung ventilation for thoracic surgery
D. H. Beck, U. R. Doepfmer, C. Sinemus, A. Bloch, M. R. Schenk and W. J. Kox

44 Recovery and neurological examination after remifentanil–desflurane or fentanyl–desflurane anaesthesia for carotid artery surgery
W. Wilhelm, N. Schlaich, J. Harrer, S. Kleinschmidt, M. Müller and R. Larsen

50 Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal
J. W. Sleigh, D. A. Steyn-Ross, M. L. Steyn-Ross, M. L. Williams and P. Smith

59 Effects of different concentrations of sevoflurane and desflurane on subcortical somatosensory evoked responses in anaesthetized, non-stimulated patients
D. J. A. Vaughan, C. Thornton, D. R. Wright, J. R. Fernandes, P. Robbins, C. Doré and M .D. Brunner

63 Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery
K. Millar, A. J. Asbury and G. D. Murray

68 Fast-track cardiac anaesthesia in the elderly: effect of two different anaesthetic techniques on mental recovery
N. P. Dowd, J. M. Karski, D. C. Cheng, S. Gajula, P. Seneviratne, J. A. Carroll Munro and D. Fiducia

77 Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy
M. H. Kim and Y. M. Lee

80 Comparison of two neurostimulation techniques for axillary brachial plexus blockade
D. M. Coventry, K. F. Barker and M. Thomson

84 Dexamethasone is a cost-effective alternative to ondansetron in preventing PONV after paediatric strabismus repair
B. Subramaniam, R. Madan, S. Sadhasivam, B. Sennaraj, P. Tamilselvan, S. Rajeshwari, D. Jagan and D. Shende

90 Comparison of effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients
A. M. Maguire, N. Kumar, J. L. Parker, D. J. Rowbotham and J. P. Thompson

94 Comparison of coagulation and blood loss during anaesthesia with inhaled isoflurane or intravenous propofol
N. L. Law, K. F. J. Ng, M. G. Irwin and J. S. F. Man

99 Decontamination of laryngoscopes in The Netherlands
M. J. L. Bucx, J. Dankert, M. M. Beenhakker and T. E. J. Harrison

LABORATORY INVESTIGATION

103 Mechanical and electrophysiological effects of thiopental on rat cardiac left ventricular papillary muscle
A. Descorps-Declère, M. P. Sauviat, K. Samii and Y. Lecarpentier

REVIEW ARTICLE

110 Lazaroids: efficacy and mechanism of action of the 21-aminosteroids in neuroprotection
R. J. Kavanagh and P. C. A. Kam

SHORT COMMUNICATIONS

120 Pharmacokinetic profile of epidurally administered methylnaltrexone, a novel peripheral opioid antagonist in a rabbit model
D. B. Murphy, H. El Behiery, V. W. Chan and J. F. Foss

122 Influence of head and neck position on cuff position and oropharyngeal sealing pressure with the laryngeal mask airway in children
K. Okuda, G. Inagawa, T. Miwa and K. Hiroki

124 Waste gas exposure to sevoflurane and nitrous oxide during anaesthesia using the oesophageal–tracheal Combitube Small Adult™
K. H. Hoerauf, T. Hartmann, S. Acimovic, A. Kopp, G. Wiesner, B. Gustorff, H. Jellinek and P. Krafft

127 Effect of two anaesthetic regimens on airway nitric oxide production in horses
D. J. Marlin, L. E. Young, R. McMurphy, K. Walsh and P. Dixon

130 Use of cisatracurium during fast-track cardiac surgery
A. Ouattara, L. Richard, J. M. Charrière, H. Lanquetot, P. Corbi and B. Debaene

CASE REPORTS

133 Successful epidural anaesthesia for Caesarean section in a patient with spondyloepiphyseal dysplasia
H. D. de Boer, A. Hemelaar, R. van Dongen and M. J. M. Gielen

135 Use of remifentanil in a patient with peripartum cardiomyopathy requiring Caesarean section
C. P. McCarroll, L. D. Paxton, P. Elliott and D. B. Wilson

138 Reduction of vasopressor requirement by hydrocortisone administration in a patient with cerebral vasospasm
J. A. Alhashemi

141 Paradoxical changes in bispectral index during nitrous oxide administration
G. D. Puri

143 Therapeutic embolization of an internal mammary artery damaged by placement of a central venous catheter
G. Abbott and P. Evans

146 CORRESPONDENCE

157 BOOK REVIEWS

159 ERRATUM

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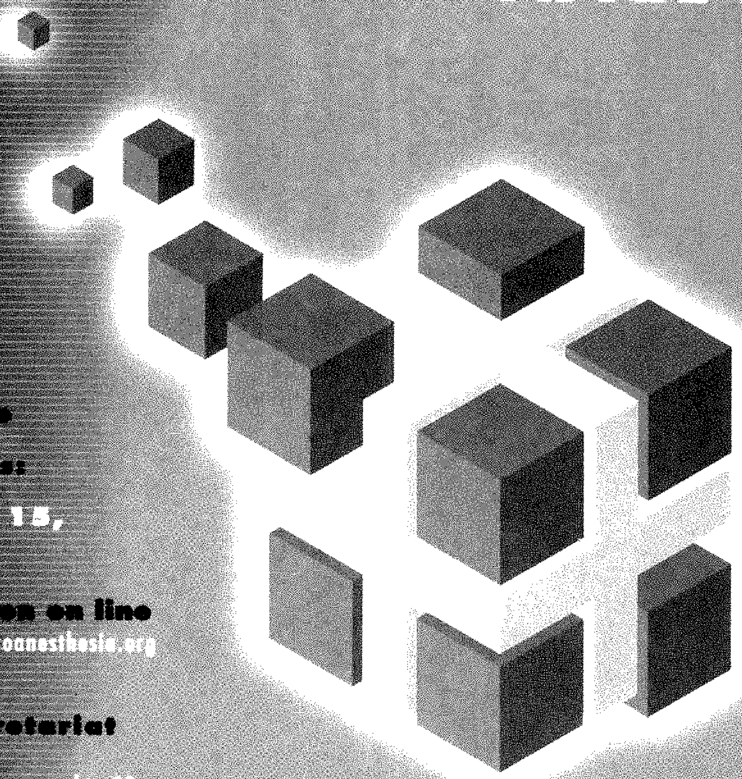

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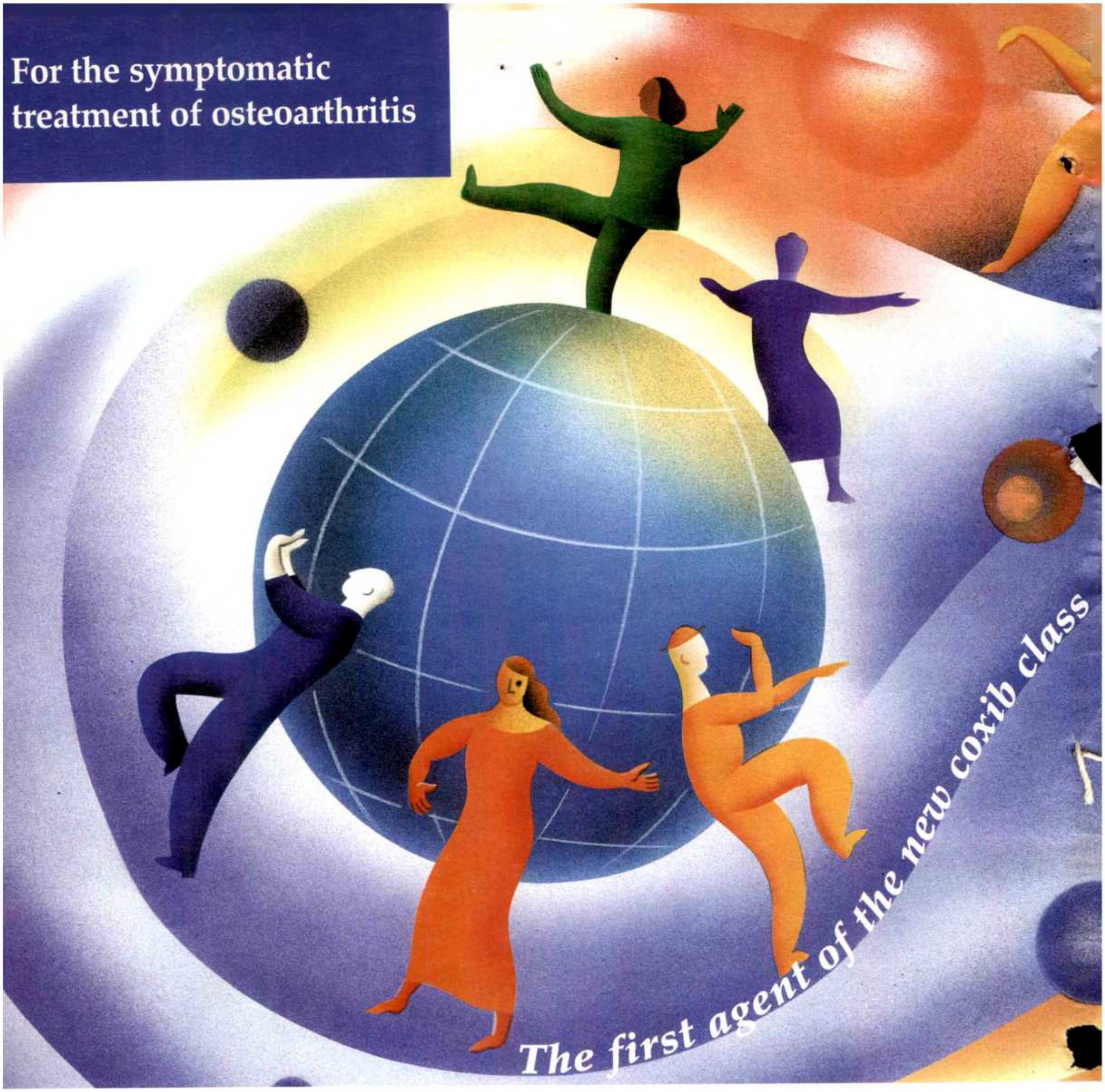
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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.
Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of

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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

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To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

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Date of preparation: February 2000

Further information: Available from:
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1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz M. *Orthopedics.* 1999;22(suppl 1):s105-s11.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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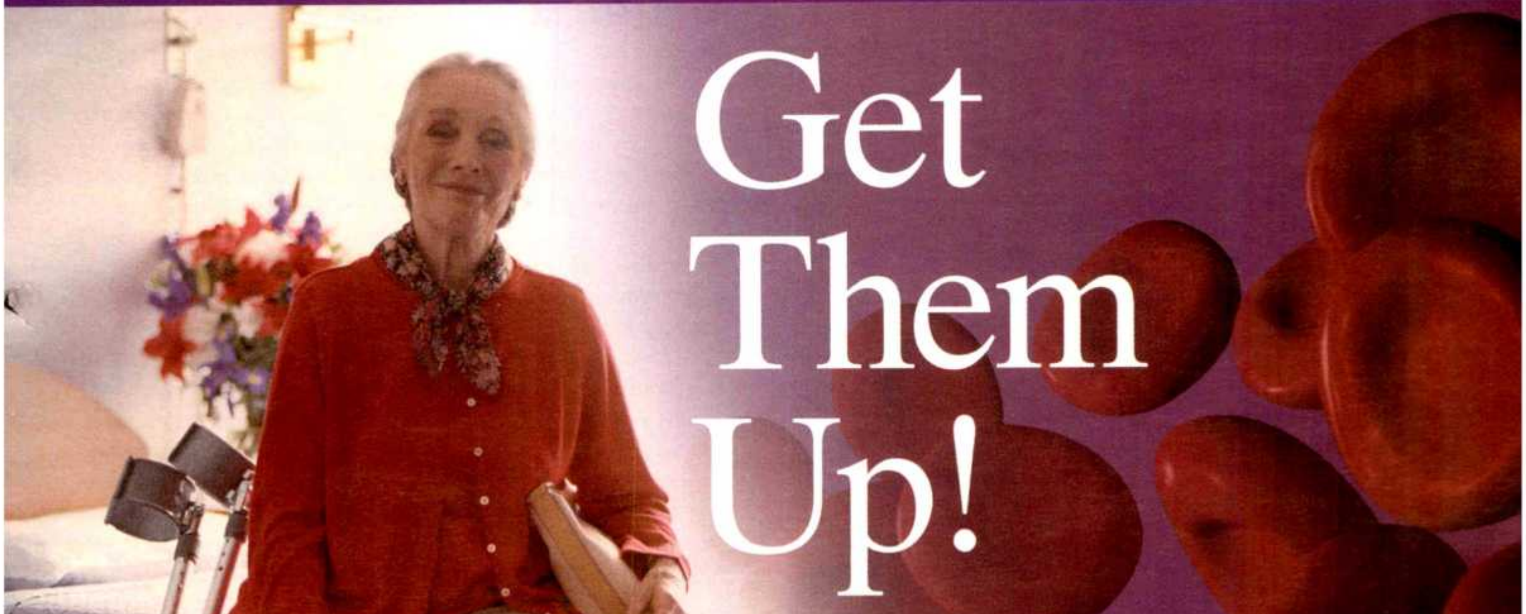

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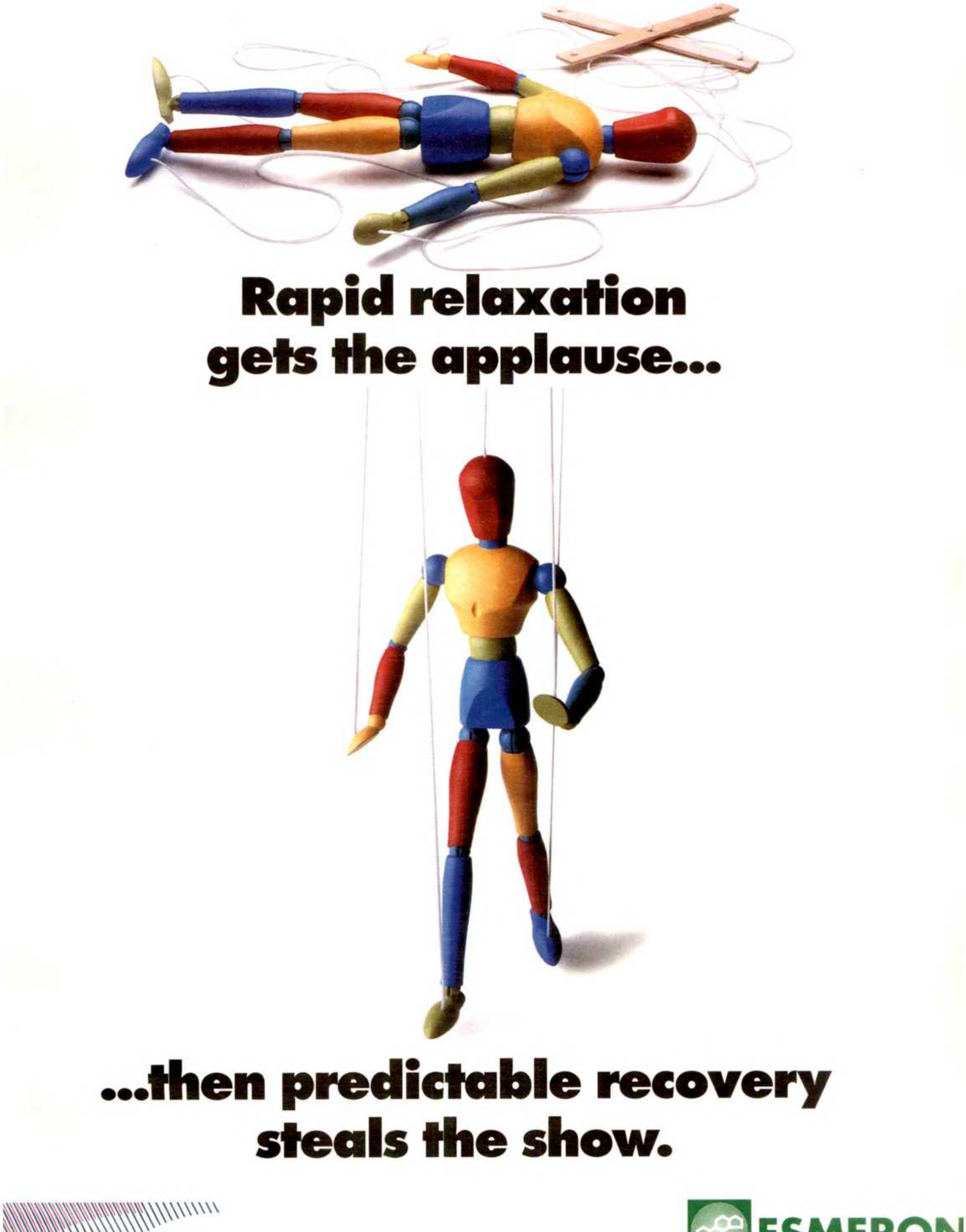

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Editorial Notices

BJA/RCA Research Grants

The *British Journal of Anaesthesia*, in conjunction with the *Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the United Kingdom.

Grants are available to support specific projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows: salaries, or items of equipment. The maximum value of any award will be £50 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will not be funding Research Fellowships with this round of awards. Applicants should note that candidates will usually be established members of academic departments of Anaesthesia in the United Kingdom; and the grant must be administered by an academic department of Anaesthesia and have the support of the Head of that Department.

For further details and forms, please **WRITE** or **e-mail** to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, OXFORD OX3 9DU *or*
john.sear@nda.ox.ac.uk

Closing date for applications is **January 19th 2001**. Late applications will **not** be considered.

Combined Scientific Meeting (CSM 2001) of The Australian and New Zealand College of Anaesthetists (Faculty of Intensive Care and Faculty of Pain Medicine) and The Hong Kong College of Anaesthesiologists

Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

5th International Conference on Memory, Awareness and Consciousness – Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, USA, June 1–3, 2001

This conference builds on the tradition of the previous Memory and Awareness in Anesthesia Conferences, and will focus on the following topics: measurement and monitoring of memory function, awareness and consciousness; interaction of anesthetic and sedative drugs with the mechanisms of consciousness, awareness and memory processes; consequences and treatment of unwanted awareness or memory function during surgery or critical care; impact of surgery, anesthesia and critical care on cognitive and psychological processes; neuroimaging and mapping of consciousness, memory, awareness and pharmacologic effects on them in the CNS.

Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

Tel: +1 212 639 6038; Fax: +1 212 772 8646.

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

12th SW Thames Anaesthesia Update

Belle Plague, French Alps, January 22–26, 2001

For further information please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT, UK. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk. Website: www.anaesthesiaupdates.com

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

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Topics include: (i) Management of end-stage respiratory failure; (ii) Mechanical support for the failing heart; (iii) Cardiac transplantation; (iv) Cardiopulmonary transplantation in children; and (v) Re-perfusion injury.

For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

Regional International Meet on Pain Management & XVIth National Society for Study of Pain

Guwahati, India, February 11–13, 2001

The conference, organized by the Assam Society for the Study of Pain under the auspices of ISSP, will be on the theme of 'Reaching out with newer perspectives'.

For further information, please contact: Pain Clinic of North East India, Opp. Bank of Baroda, G.S. Road, Bhangagarh, Guwahati 781005, India. Tel: +91 361 548191; Fax: +91 361 511927; E-mail: issp2001@usa.net

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Neuroanaesthesia Society of Great Britain and Ireland

Churchill College, Cambridge, UK, March 29–April 1, 2001

The Neuro Update Course takes place on March 29–30, 2001. The NAS meeting 2001 takes place March 31–April 1, 2001

For further information on the meeting please visit our website: www.nas.dundee.ac.uk or contact: Conference Secretary (NAS 2001), Department of Anaesthesia, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. Tel: +44 1223 217897; Fax: +44 1223 217223; E-mail: christine.butler@msexc.addenbrookes.anglox.nhs.uk

Advances in Objective Assessment of Hand/Upper Extremity Function and Outcome

Genval (Brussels), Belgium, April 20–21, 2001

For further information please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail:fschuind@ulb.ac.be

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, England, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
Tel: 01442 879000. Fax: 01442 870999.

E-mail: enquiries@prestige-promotions.co.uk

5th International Conference on Memory, Awareness and Consciousness: Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, NY, June 1–3, 2001

For further information, please contact: (for scientific enquiries) Ruth Reinsel, PhD, Department of Anesthesiology and Critical Care, Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6038; Fax: +1 212 772 8646; E-mail: mac@mskcc.org; website: www.maacc.org or (for other enquiries) Office of Continuing Medical Education, Box 31, Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6754; Fax: +1 212 717 3140; E-mail: cmeinfo@mskcc.org; website: www. mskcc.org

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92; E-mail: SSAI.2001@rito.no
Web site: www.ssai2001.org

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: **(Deadline – November 1, 2001)** Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 86, Number 1, January 2001

Editorial I

Can we characterize the central nervous system actions of α_2-adrenergic agonists?

Resurgence in interest in α_2-adrenergic agonists has been fuelled by the emergence of dexmedetomidine, the latest α_2-agonist to be developed. Recently licensed in the USA, it has prompted many to re-examine more closely the workings of this fascinating class of drug and thereby its clinical applications. Clonidine, the prototype α_2-agonist, was originally developed in the early 1970s for its potential use as a nasal decongestant. It rapidly found favour as a useful anti-hypertensive agent;[1] however, with the advent of the ACE inhibitors and more selective β-adrenergic antagonists, clonidine has been relegated to no better than a third line alternative for this purpose. It has, however, remained an intriguing compound that has been shown to be efficacious in a wide range of applications, from analgesia,[2] sedation and reduction in post-operative shivering,[3] to the control of symptoms during alcohol[4] and nicotine[5] withdrawal. In this issue of the journal, Hall and colleagues report their findings of a study specifically designed to quantify the dose response of low-dose clonidine in healthy volunteers with regard to sedation, analgesia and cognition.[6]

While much work has been published pertaining to the use of clonidine as an adjunct to anaesthesia and pain management, few reports address its specific use as a sedative unrelated to anaesthesia. Its use as a sedative/anxiolytic in the intensive care setting is now relatively commonplace, particularly after long-term sedation with opiates and/or benzodiazepines. Evidence does exist to show that clonidine is efficacious in the relief of withdrawal symptoms from these agents.[7 8] However, reliable data on i.v dosing, sedative efficacy and the effect on outcome in the intensive care setting are lacking.

This paper, together with a recently published manuscript by the same group addressing the same questions for dexmedetomidine[9], begins to fill the gaps although there are several reasons why data collected from young healthy volunteers cannot readily be extrapolated to patients in intensive care. First, there are two adverse effects that need to be considered. Bradycardia can be seen after acute administration of α_2-agonists, an effect that is thought to be mediated by a centrally mediated reduction in sympathetic tone, together with an increase in vagal tone. In this paper, the loading dose of clonidine is given over a 15-min period, thereby lessening the risk of acute bradycardia. If there is a need to administer the drug faster, bradycardia can be pre-empted by the administration of an anticholinergic agent. Hall and colleagues point out that volunteers consistently complained of mouth dryness after clonidine administration and this could be potentially clinically significant in the intensive care setting. The addition of an anticholinergic (to avoid bradycardia) could compound this problem further. Second, as with nearly all drugs that are receptor agonists, one would expect to see desensitization after prolonged exposure to clonidine and its corollary, 'rebound'. Indeed there have been reports of acute hypertensive crises occurring after the abrupt cessation of clonidine therapy.[11] If clonidine infusions are used in intensive care for long periods it is to be expected that abrupt cessation of therapy would also have to be carefully monitored.

Third, in the intensive care setting, there are likely to be complex interactions with coincident administration of opioid and cholinergic receptor ligands making determination of the mechanisms between adrenoreceptor agonists and effect difficult. For example clonidine, at doses providing significant analgesia, has been shown to cause an increase in the release of acetylcholine from the dorsal horn of the spinal cord in sheep.[11] Concurrent administration of neostigmine enhances this analgesic effect.[12] Areas containing dense populations of α_2-receptors have been demonstrated in the substantia gelatinosa of the human spinal cord,[13] often in close association with μ-opioid receptors. Again, α_2-agonist-mediated analgesia can be enhanced in the presence of μ-agonists.[14] Will similar interactions and synergy occur supraspinally? The MAC-sparing effect of i.v. and oral clonidine has been well documented[15 16] and as such again provides further evidence for their complex interactions with other CNS depressants.

Hall and colleagues have commented on the unique feature of rousability seen with low dose clonidine (and other α_2-agonists[9]), whereby even apparently deeply sedated subjects (as evidenced by Bispectral Index (BIS)

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monitoring) can be fully aroused and show little or no impairment in psychomotor performance. Arousal can be defined as the state of physiological reactivity of a subject, ranging from sleep to panic. It has been suggested that a dual-level control mechanism exists with a passive low-level physiological arousal system being modulated by active cognition. Investigators studying the neural correlates underlying sedation (as opposed to anaesthesia) have focused on the mechanisms underlying arousal and attention (as opposed to anaesthesia or sedation). Arousal level is regulated by many neurotransmitter systems found in a wide variety of areas of the brain. Norepinephrine release affects both attention and arousal in a complex manner; it is speculated that noradrenergic systems are more involved with the active cognitive modulation of arousal. Smith and Nutt[17] have described how, after administering clonidine to volunteers and asking them to perform a simple task many lapses of concentration were seen when the subjects were left quietly alone. These lapses of concentration were almost fully reversed by arousing noise and by idazoxan, an α_2-antagonist, and may be illustrative of the differing modulatory effects of norepinephrine depending on the underlying arousal level of the subject. Pre-synaptic inhibition of norepinephrine release by α_2-agonists leads to reduced levels of arousal. Idazoxan has been shown to speed up response times in certain situations and reverse the sedative effects of clonidine;[18] externally stimulating the subject (for example with loud noise) has the same effect. It is speculated that arousing subjects causes increased release of central norepinephrine, thereby chemically antagonizing the effects of clonidine. Once the subject is left quietly alone, norepinephrine release decreases and the sedative effects of clonidine once again become apparent.

Coull and colleagues compared subjects' performance of a simple task while sedated with diazepam or clonidine and found that in certain situations the subjects sedated with clonidine were both able to successfully complete the test task and in some cases their performance was enhanced (when compared with placebo).[19] One theory behind this observation is that when the subject is aroused, they begin to focus their attention on the task at hand. Increased release of norepinephrine in areas of the brain specifically required to perform the task momentarily antagonizes the effect of clonidine. While in other areas of the brain the clonidine effect is still apparent, perhaps obtrunding the subjects' response to distracting or unnecessary inputs. Another explanation may lie in the fact that the dose–response curve of α_2-agonists is complex. For example clonidine attenuates noradrenergic activity at low doses (because of the highly efficacious pre-synaptic action), but enhances activity at higher doses. It is thus clear that central α_2-agonist sedation is not a result of a global reduction in cerebral activity. This is to be expected as the distribution of α_2-receptors within the brain is not at all uniform, with areas such as the thalamus and locus coeruleus (an important modulator of vigilance) containing very high concentrations of noradrenergic neurones[13] compared with other regions of the brain.

These studies raise a number of interesting issues regarding the depth and quality of sedation. The Ramsay score forms the basis of most commonly used sedation scoring systems, relying on the patient's response to stimulation (verbal and/or tactile). If patients sedated with low doses of α_2-agonists can be easily aroused to full 'consciousness' from a state of deep sleep, it makes assessment of sedation using this system impossible. Hall and colleagues have used three methods of sedation assessment consecutively and all three scores mirror this phenomenon of rousability, including BIS values returning to almost baseline levels during arousal. The use of the BIS to monitor the level of sedation with other agents has been well validated, and it is interesting to see that similar results are produced under sedation with clonidine. Therefore, in order to assess the sedative state in patients receiving α_2-agonists a new method of sedation assessment is needed. Indeed, are such patients really sedated, if they can be so fully aroused by external stimuli? In what situations would this feature be an advantage? Certainly there are scenarios in which this could be a distinct disadvantage, such as when patients are subjected to painful or unpleasant procedures. However, in situations where patient co-operation is desirable or needed, it may prove most useful. For example, sedated patients in the intensive care setting can be called upon to co-operate with the physiotherapist (by focusing on a task) and then fall back to sleep when left undisturbed.

A review on α_2-agonists from last year[20] describes the many benefits of clonidine use in anaesthetic practice. Why then is it not used more frequently? Clonidine is licensed, (and therefore only marketed), for the treatment of hypertension, migraine prophylaxis and menopausal flushing. Lack of familiarity, availability and fear of side effects are additional reasons. Clonidine has a spectrum of action that goes beyond the effects described in this paper, including a decrease in insulin release,[21] inhibition of renin release[22] and a decrease in intra-ocular pressure[23] to name but a few. The activation of α_1 receptors at higher concentrations widens its spectrum of activity. Establishing which of the three α_2-adrenoceptor subtypes (α2a, α2b and α2c) are responsible for which effects, may lead to the development of novel agents that are selective for individual receptor subtypes. These can then be administered to achieve the desired effects without producing unwanted side effects. The newer α_2-agonist, dexmedetomidine, being more highly specific for the α_2-adrenoceptor, goes some way to achieving this ideal and is specifically licensed for use as a sedative agent in the USA. This paper provides a starting point for furthering our understanding of how, possibly clonidine, and probably new, specific α_2-agonists can best be used in ways that ultimately could improve patient care.

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Editorial II

Publishing changes in 2001

Peer-reviewed journals that are predominantly archival tend to be viewed as rather conservative and staid organs but they do provide an accurate reflection of changes in modes of communication and they adapt, at varying speeds, to meet the needs of the audiences which the journals are designed to serve.

From its inception in 1923 until 1995, the sole method by which the *British Journal of Anaesthesia* conveyed information to subscribers was via the printed page. However, in the last decade, there have been two significant changes in our *modus operandi*. In 1995, material was distributed on a CD–ROM and, since July 2000, the *BJA* has been published on the Internet.

In partnership with *Anesthesia and Analgesia,* the *BJA* helped to pioneer the development of the Electronic Anesthesia Library (TEAL). Shortly after linking with

Anesthesia and Analgesia, the two journals were joined by *Anesthesiology* and the *Canadian Journal of Anaesthesia* and so, in 1995, all four journals became available in a single format. TEAL comprises a CD–ROM containing all the peer-reviewed material appearing in these four journals over a 5 yr period. Five volumes have now been published, spanning the period 1991–1999. This superb archive obviates the necessity for storage and binding of journals and it allows instantaneous access via an easily used search engine to the majority of the most highly cited anaesthetic papers in the literature. From this year, TEAL will be produced not only on CD–ROM but also in a DVD–ROM version; both formats will be available for at least another 3 years. The advantage of the DVD–ROM is that it will be able to carry the contents of all four journals for a decade on a single DVD.

The second and most revolutionary change in communication has been via the Internet; many journals now publish their contents via this medium. The *BJA* became available in July 2000 on the Internet with free access until December 2000. However, from January 2001, access is restricted to subscribers by the use of a password whilst occasional users may access it on a 'pay-as-you-view' basis.

Another major initiative, which the *BJA* will launch in 2001, is the introduction of a new journal of continuing educational and professional development (CEPD) called *BJA: CEPD Reviews*.The Editor-in-Chief of this journal is Professor David Rowbotham and the chairman of its new Editorial Board, separate from that of the *BJA*, is Dr Ralph Vaughan. The *raison d'être* for this venture is that the *BJA*, as the official journal of The Royal College of Anaesthetists (RCA), has responsibilities in producing CEPD material for Fellows, Members, and also trainee anaesthetists undertaking the RCA training programme. In the UK, the RCA stipulated in April 2000 that participation in CEPD was obligatory for all career-grade anaesthetists. CEPD is also an essential element of clinical governance and will be an integral and mandatory part of the General Medical Council's (GMC) Revalidation Folder (Personal Portfolio). The GMC aims to finalize its proposals for revalidation by May 2001. If these prove to be acceptable, as anticipated, a system will be introduced in the UK whereby every 5 yr doctors will be obliged to undergo revalidation; a doctor who fails the revalidation procedure will be liable to erasure from the *Medical Register*, i.e. will be unable to practise medicine either as a specialist or as a generalist. Thus whilst participation in CEPD has always been a normal part of doctors' professional activities, it will soon become a legal necessity.

BJA: CEPD Reviews intends to cover essential core material in the fields of anaesthesia, critical care medicine and pain management. It will comprise a series of review articles of a predominantly teaching nature rather than of a comprehensive research format. It will be published bimonthly, commencing in February 2001. *BJA: CEPD Reviews* will be distributed to those individuals on the RCA list (Fellows, Members and trainees) as part of their College subscription. However, it is anticipated that the review will have widespread appeal to anaesthetists worldwide wishing to keep abreast of CME via up-to-date teaching review material. Material published in this new review journal will be citable with the title of *BJA: CEPD Reviews* and pagination differing from that in the full *BJA*.

Another innovation introduced by the *BJA* in 2001 is the production of a précised version of the full journal, termed the *BJA Concise*. This version contains full text of editorials, reviews (research reviews), book reviews, correspondence and commentaries together with abstracts only of peer-reviewed original articles and case reports. *BJA Concise* is circulated only to anaesthetists on the RCA list. Other subscribers will continue to receive the full version of the *BJA* and all subscribers, those affiliated with the College and non-affiliated and institutional subscribers, will obtain access to the full version of the *BJA* on the Internet by the use of a password obtained as part of their subscription arrangements. Separate subscription arrangements have been made for individuals on the College list who still require full paper copy of the journal rather than the *BJA Concise*. Material in *BJA Concise* will be paginated and cited identically to that in the full *BJA*.

There has been much discussion in the lay press that the technological revolution in communication that has occurred in the last decade exceeds the changes wrought by the first industrial revolution. However, there still remains a substantial number of our subscribers either without Internet access or for whom access is extremely slow or delayed because of problems with local telecommunications. We hope, therefore, that the changes described above will enable a high standard of anaesthetic literature to be delivered in appropriate format to both technophiles and those with limited electronic availability. At the same time, with the publication of *BJA: CEPD Reviews*, we are responding in part to the increasing demand placed by the public on anaesthetists to demonstrate their maintenance of competence to practice. There is, however, little doubt that the reader will see continuing changes as the journal adapts progressively to the varied demands of its widening audience, and its role as official journal of the RCA with its responsibilities for maintenance of professional standards.

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BJA

CLINICAL INVESTIGATIONS

Sedative, analgesic and cognitive effects of clonidine infusions in humans[†]

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This placebo-controlled, randomized study evaluated, on separate days, the dose–response relationship for 1 h infusions of clonidine 1, 2 and 4 $\mu g\ kg^{-1}\ h^{-1}$, in eight healthy volunteers aged 22–30 yr. Response end-points included sedation (bispectral index, visual analogue scale and observer assessment of sedation), analgesia to a cold pressor test, memory (recall of word lists), cognitive function (digit symbol substitution test (DSST)), respiratory function (respiratory rate, end-tidal carbon dioxide, oxygen saturation) and haemodynamic stability (heart rate and mean arterial pressure). Clonidine infusions resulted in significant and progressive sedation, but all subjects were easily awoken to perform tests and evaluations. Statistically significant analgesia, memory impairment and reduced performance on the DSST occurred during 4 $\mu g\ kg^{-1}\ h^{-1}$ infusions (resulting in a plasma concentration of 2 $ng\ ml^{-1}$. There were no statistically significant changes in cardiorespiratory variables throughout the study.

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Keywords: sedation; analgesics, α_2-adrenoceptor agonist, clonidine

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Unlike most other sedative drugs, α_2-adrenoceptor agonists are capable of producing both sedation and analgesia and result in little, if any, respiratory change.[1] This combination makes them potentially useful in the postoperative, non-ambulatory setting, especially in high-dependency and intensive care situations. With the development of the new α_2-agonist dexmedetomidine, there has been a resurgence of interest in the use of this class of drugs for sedation purposes.[2 3]

An important difference between clonidine and dexmedetomidine is their elimination half-life, which is nearly four times longer for clonidine than for dexmedetomidine.[4] Therefore, dexmedetomidine is more titratable than clonidine, and recovery is more rapid.[2] However, slower elimination may sometimes be desirable, especially in the intensive care situation, where a more gradual weaning from sedation and analgesia might be desired or beneficial.

Continuous i.v. clonidine has been evaluated for its morphine-sparing effects in treating postoperative pain,[5 6] and in the postoperative period for complete pain control.[5] One notable finding in these studies was a substantial haemodynamic effect (hypotension and bradycardia) coincident with the desired sedative and analgesic effects. In addition, these studies provided little information about the dose–response relationship for analgesia, sedation and haemodynamic effects. The present placebo-controlled study in healthy volunteers evaluated three doses of clonidine that were predicted to have minimal cardiovascular effects, and evaluated several end-points, including sedation, cognitive function, analgesia and cardiorespiratory function.

Methods

With Institutional Review Board approval, eight subjects provided their written consent to participate in the study. Volunteers were 22–30 yr of age, ASA grade I, and of both genders. They were given a brief physical examination,

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[†]This article is accompanied by Editorial I.

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along with a urine pregnancy test as appropriate. They were excluded if there was a history of asthma requiring treatment or any contraindication to α_2-adrenoceptor agonists, if their ideal body weight was greater than 20% of normal, or if they were unable to complete psychomotor tests.

Subjects were asked to abstain from alcohol for 24 h and any oral intake for 6 h before the study. Each volunteer participated on four occasions separated by at least 7 days, but not more than 10 days. They were randomized to either placebo or one of three doses of clonidine. Treatments consisted of a loading dose of placebo or clonidine, 1, 2 or 4 $\mu g\ kg^{-1}$, given over a 15 min period and followed by a maintenance infusion of placebo or clonidine, 1, 2, or 4 $\mu g\ kg^{-1}\ h^{-1}$, for a 45 min period. Monitoring involved ECG leads II and V_5 for monitoring heart rate (HR) and cardiac conduction changes, non-invasive oscillometric arterial pressure measurement (mean arterial pressure, MAP), pulse oximetry for oxygen saturation (Sp_{O_2}), and a nasal cannula for end-tidal carbon dioxide monitoring. The depth of hypnosis was monitored with a processed EEG (bispectral index system, BIS; Aspect Medical Systems, Newton, MA, USA). Two i.v. lines were placed in the non-dominant arm, one for infusion of clonidine and the other in a different vein for sampling for plasma clonidine concentration. The dominant hand was used to perform written tests and for immersion into ice water (cold pressor test).

After instrumentation and a 10 min rest period, baseline measurements (HR, MAP, Sp_{O_2}, carbon dioxide and BIS) were collected. This was followed by a 5 min rest period, after which resting haemodynamics and end-tidal carbon dioxide were averaged during a 3 min sampling period. There followed the battery of tests to assess sedation, psychomotor performance and memory, and the cold pressor test. After all the baseline measurements and tests had been done, infusions were started with both investigators and subject blinded to the randomization code. Cardio-respiratory parameters were measured at the end of the loading dose (15 min), the end of infusion (60 min) and at 45 and 90 min of recovery, as well as during all cold pressor tests. BIS was recorded every 5 min throughout infusion and recovery. Assessments of sedation (Observer Assessment of Analgesia/Sedation (OAA/S) and a visual analogue scale for sedation ($VAS_{SEDATION}$)) and a self-rating of co-ordination (visual analogue scale for coordination ($VAS_{COORDINATION}$)) were taken at 5, 10 and 15 min during the loading dose and again at 60 min, just before drug termination. Psychomotor (Digital Symbol Substitution Test, DSST), cold pressor and memory tests were performed only at the end of the 60 min infusion period. After drug termination, all tests and assessments were repeated at 45 and 90 min of recovery.

Description of tests

There were three measures of sedation. The first was objective and measured from the processed EEG signal, which indicated the state of hypnosis (BIS). This was recorded continuously and noted at 5 min intervals throughout the study. The second measure was assessment by an independent observer (OAA/S) and was based on categories of responsiveness to verbal stimuli, speech, facial expression and eyes. Finally, visual analogue scales (VAS, scale 0–100) were used to assess sedation and coordination by sliding a movable indicator line between the two end-points of the scale. The subject rated the level of sedation ($VAS_{SEDATION}$) on a scale in which the 0 end represented 'asleep' and 100 represented 'wide awake'; the coordination scale ($VAS_{COORDINATION}$) had the descriptors 'clumsy' at 0 and 'well coordinated' at 100.

Psychomotor performance was tested using a DSST and memory function was determined from a word recall test (MEM). The DSST is a timed test of psychomotor performance (a different test form is given at each time point) with a chart of eight rows of digits in random sequence. There are nine written symbols, each with a corresponding numerical digit. The subject replaces the symbol with its corresponding number. Correct substitutions within a 90 s period were tallied for the score. The MEM test consisted of listening to a series of 16 unrelated words and immediately reciting as many as possible. The MEM test at the 90 min recovery point was different. Subjects did not listen to a new series of words, but rather they were asked to recall as many of the words as possible from the three previous lists, which had been given at baseline, 60 min of infusion and 45 min of recovery. This test is termed the comprehensive memory test (CMEM). In addition to tallying the total number recalled, the number recalled from each list was identified.

The cold pressor test consisted of immersing the subject's hand to the wrist in a constantly agitated ice/water mix for 1 min, and collecting haemodynamic variables and averaging them over the last 15 s of the test. Pain experienced due to the cold exposure was assessed by the subject using a visual analogue scale (VAS_{PAIN}) that had end-points of 'no pain' (0) and 'worst pain imaginable' (100).

Statistics

Data are expressed as mean (SD) except in graphical presentations, where standard error bars are used to reduce clutter. Repeated measures analysis of variance (ReANOVA) was used and *post hoc* analysis was with the Bonferroni test. The CMEM was a single test (not repeated over time), so Student's *t*-test was used to determine differences between groups. Significance was established at $P<0.05$.

Results

Eight healthy subjects (four men and four women aged 22–30 yr) were enrolled. The eight subjects had a mean weight of 71 kg (range 50–84 kg) and a mean height of

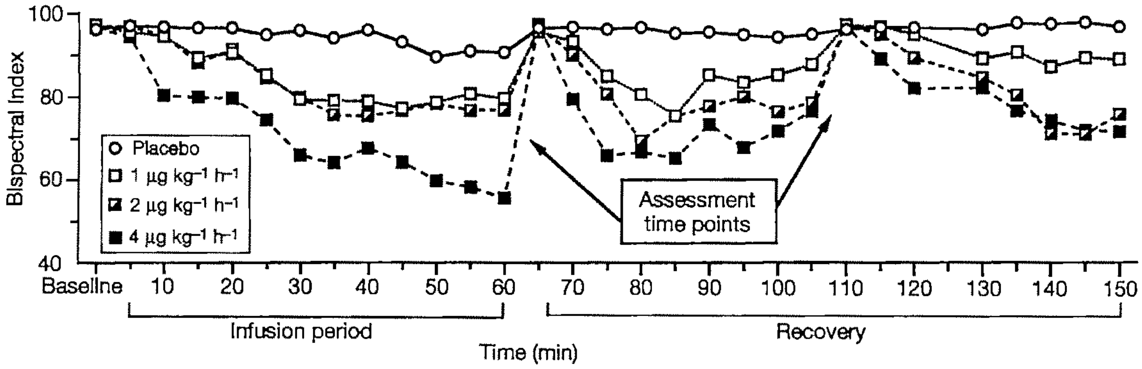

Fig 1 Group results (means) of bispectral index (BIS) numbers recorded every 5 min during the 60 min infusion and 90 min recovery periods in eight volunteers.

165 cm (range 146–180 cm). Mean (SD) plasma clonidine concentrations achieved at 15 and 60 min respectively of each 1 h of clonidine infusion were 0.34 (0.1) and 0.25 (0.1) ng ml^{-1} for 1 μg kg^{-1} h^{-1}, 0.81 (0.4) and 0.84 (0.2) ng ml^{-1} for 2 μg kg^{-1} h^{-1}, and 2.0 (0.9) and 1.96 (0.5) ng ml^{-1} for 4 μg kg^{-1} h^{-1}.

Sedation assessment

All three doses of clonidine produced significant sedation (BIS) compared with placebo (Figs 1 and 2). There was increasing sedation with increasing dose, but the BIS was unable to differentiate between 1 and 2 μg kg^{-1} h^{-1}. After the 60 min infusion, the BIS number had decreased by 6, 17, 21 and 62% in placebo, 1, 2 and 4 μg kg^{-1} h^{-1}. At 90 min recovery from clonidine 1 μg kg^{-1} h^{-1}, the BIS had returned to baseline concentrations, but 90 min after the 2 and 4 μg kg^{-1} h^{-1} infusions there were still significant concentrations of sedation based on BIS. The OAA/S gave essentially identical results to the BIS during both infusion and recovery. Only slightly different results from the VAS$_{\text{SEDATION}}$ tests were noted; a 23, 57, 60 and 84% reduction in score was recorded at the 60 min infusion time point for the four groups respectively. This test did not provide a statistically significant difference between placebo and clonidine 1 μg kg^{-1} h^{-1}, though it did show a difference between placebo and clonidine 2 and 4 μg kg^{-1} h^{-1} and a similar recovery profile to the BIS and OAA/S.

Cognitive function and coordination

Although immediate memory recall decreased after the 60 min infusion by 12, 25, 25 and 45% in the four groups respectively, the only significant difference was noted in the placebo versus clonidine 4 μg kg^{-1} h^{-1} comparison (Fig. 3). The CMEM of total recall of the three previous word lists, given at 90 min recovery, indicated that the 4 μg kg^{-1} h^{-1} dose significantly impaired recall of the list heard after the 60 min infusion compared with placebo (33% recall after placebo; 7% recall after clonidine 4 μg kg^{-1} h^{-1}). Recall of the list given at the 45 min recovery period was not significantly impaired after clonidine infusion (Fig. 3). During placebo, recall increased from baseline so that the most words were recalled from the most recent list. This

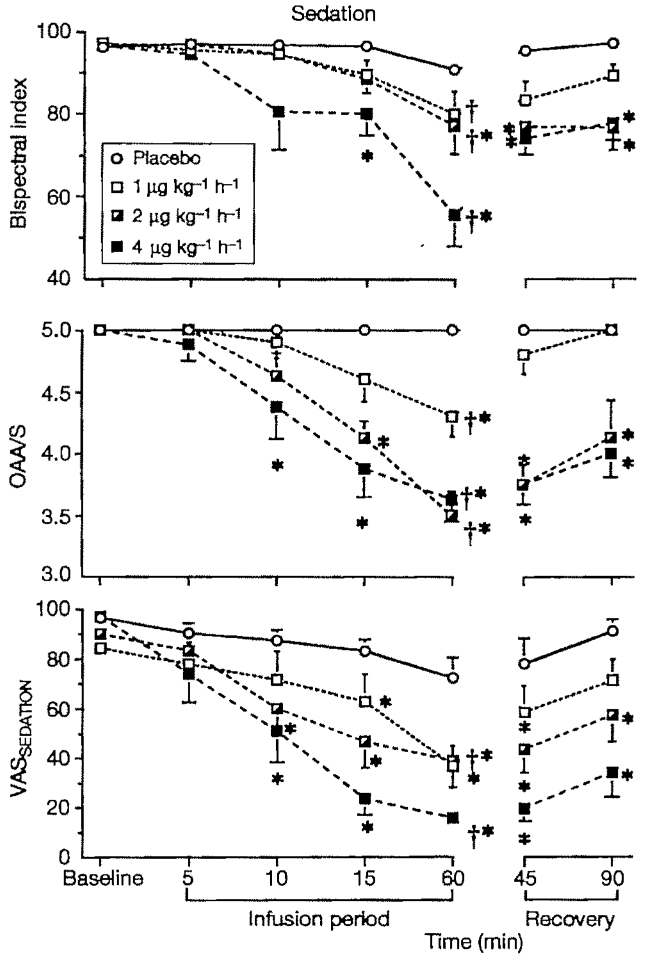

Fig 2 Results of sedation tests indicate that there were progressive increases in sedation with increasing dose of clonidine. There were significant differences by ReANOVA (†) compared with placebo for the 2 and 4 μg kg^{-1} h^{-1} doses for all tests of sedation. In addition, specific time points were compared with baseline with Bonferroni *post hoc* analysis *$P<0.05$.

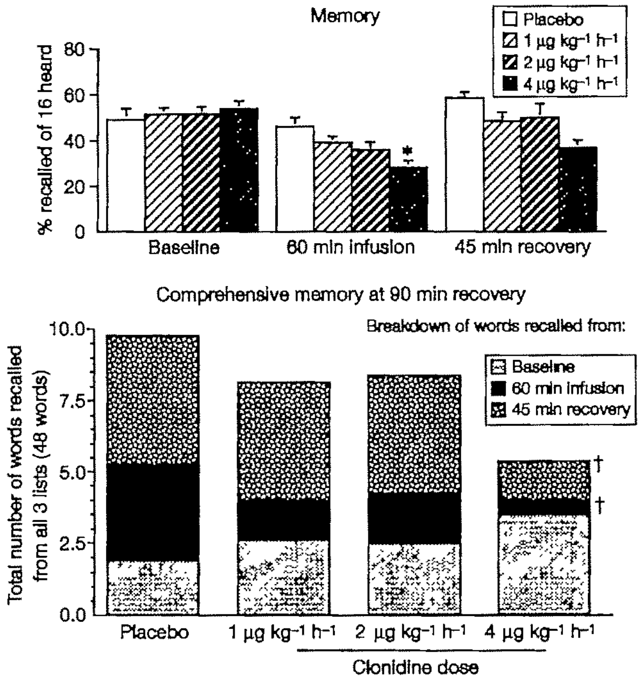

Fig 3 (Upper graph) Percentages of words recalled in the three 16-word memory tests given at baseline, after 60 min of infusion and 45 min into recovery. Only the clonidine 4 µg kg^{-1} h^{-1} infusion resulted in significant impairment in memory. $*p<0.05$ compared to placebo. (Lower graph) The 90 min recovery comprehensive memory test, in which subjects were asked to recall as many of the words as possible from the lists presented previously. The total number of recalled words and the list from which the word originated are shown. The total number of words recalled was greatest in the placebo group, whose recall increased from baseline, so that the most words were recalled from the most recent list. This progression did not persist in the clonidine groups, primarily because of the volunteers' inability to recall words presented during the infusion periods. This was particularly true during the 4 µg kg^{-1} h^{-1} infusion, when only two (of 16) words were recalled. $^{\dagger}P<0.05$ compared to placebo.

pattern was not observed in the clonidine infusion groups. There was no evidence of retrograde amnesia, as the recall of the baseline list (presented before infusion) was not different between the placebo and clonidine infusions groups.

We were unable to identify significant differences from placebo in DSST performance during the 60 min infusion test except at clonidine 4 µg kg^{-1} h^{-1} (Fig. 4). Decreases in the DSST at 60 min in the placebo and clonidine 1, 2 and 4 µg kg^{-1} h^{-1} infusion groups were 0, 5, 21 and 40% respectively. When compared with the respective baseline tests, the DSST performance was significantly changed in the 4 µg kg^{-1} h^{-1} group after the 60 min infusion and throughout recovery. The volunteer's assessment of coordination on a VAS paralleled the DSST impairment at the 4 µg kg^{-1} h^{-1} dose.

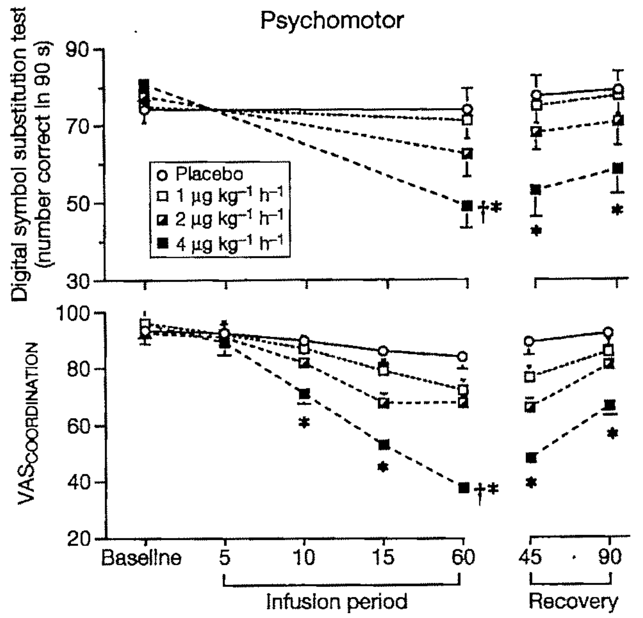

Fig 4 Visual analogue scale (VAS) for coordination, as evaluated by the volunteers, and the 90 s timed digital symbol substitution test (DSST). Significant impairment was found in the clonidine 4 µg kg^{-1} h^{-1} group, but no significant changes were seen in the other groups. †Results of ReANOVA; *comparison of specific time points from baseline responses ($P<0.05$).

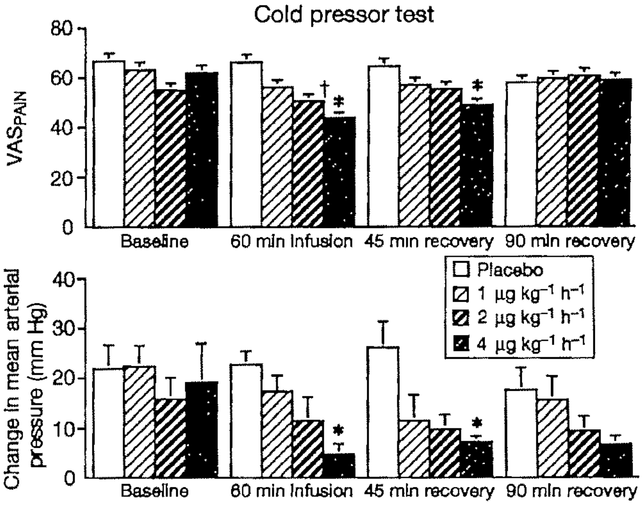

Fig 5 With increasing doses of clonidine, there was a trend for the cold pressor test to elicit smaller increases in mean arterial blood pressure and pain scores. Significance was achieved, in terms of reduction in blood pressure and the pain response, at the 4 µg kg^{-1} h^{-1} infusion rate ($*P<0.05$). The attenuation of the arterial pressure response and the pain response persisted through 45 min of recovery. †Significant difference between groups.

Cold pressor test

Compared with placebo, VAS$_{PAIN}$ during cold pressor test decreased progressively from baseline with increasing clonidine infusion doses but was significant only at 4 µg kg^{-1} h^{-1} (Fig. 5). In addition, clonidine 4 µg kg^{-1} h^{-1} produced significantly more analgesia than 2 µg kg^{-1} h^{-1}. There was a 29% decrease in pain score during the 4 µg kg^{-1} h^{-1} infusion, but no analgesia was retained in

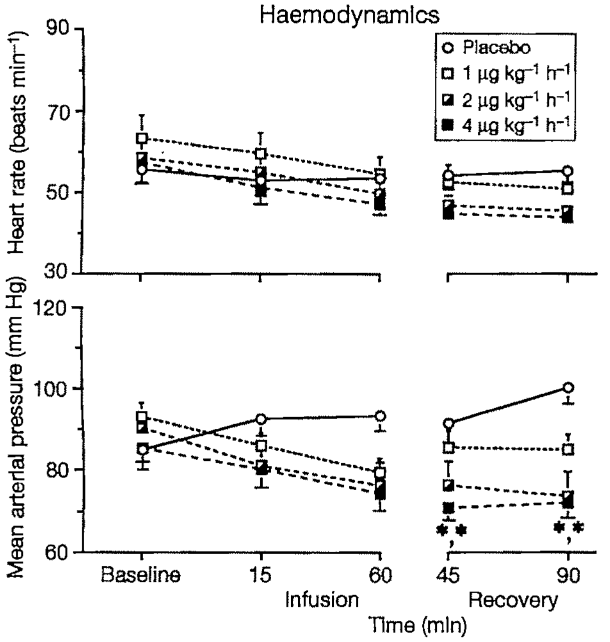

Fig 6 The haemodynamic responses to infusion of clonidine and placebo. The data suggest that clonidine lowered arterial pressure whereas placebo raised it, but statistically significant differences were not achieved between groups during the infusion periods. Similarly, heart rate showed no significant changes over time compared with baseline. $*P<0.05$ compared to baseline.

the recovery period. The MAP response during the cold pressor test after the 60 min infusion increased by 4% in placebo but decreased by 23, 31 and 74% during clonidine 1, 2 and 4 µg kg^{-1} h^{-1} infusions respectively. This decreased response was significant in the 4 µg kg^{-1} h^{-1} group and had recovered by the 90 min recovery.

Cardiorespiratory effects

We found small but not statistically significant differences in the MAP response to clonidine compared with placebo (Fig. 6). After the 60 min infusion, MAP had increased by 10% in the placebo group and decreased by 15, 22 and 13% in the clonidine 1, 2 and 4 µg kg^{-1} h^{-1} groups respectively. In the recovery period, MAP was significantly reduced from baseline concentrations in the 2 and 4 µg kg^{-1} h^{-1} infusion groups. This reduction was still 15–24% below baseline at the 90 min recovery time point. The heart rate decreases of 2, 13, 15 and 18% observed during the infusions and recovery in placebo and clonidine 1, 2 and 4 µg kg^{-1} h^{-1} respectively were not significant and were similar. Respiratory rate (mean 13 b.p.m.), end-tidal carbon dioxide concentration (mean 36 mm Hg) and oxygen saturation (mean 99%) did not change in any group during the course of the study. For example, end-tidal carbon dioxide at baseline, after 1 h of clonidine and after 90 min of recovery for placebo was 39 (1), 39 (2) and 39 (2) mm Hg respectively, and for clonidine 4 µg kg^{-1} h^{-1} it was 37 (1), 38 (2) and 37 (2) mm Hg. Furthermore, haemoglobin oxygen saturation was similar at the same time points (placebo, 99 (1), 99 (1), 99 (1); clonidine 4 µg kg^{-1} h^{-1}, 99 (1), 98 (1), 99 (1)).

Discussion

The present study documents dose-dependent sedation by i.v. infusion of clonidine. Analgesia, suppression of the arterial pressure response to the cold pressor test, memory impairment and significant decreases in psychomotor performance were observed only when clonidine was infused at 4 µg kg^{-1} h^{-1}, and were associated with plasma concentrations of 2 ng ml^{-1}. However, our study was of only eight volunteers and thus of relatively low power. Although MAP and heart rate tended to decrease during clonidine infusions, these changes were not significant.

With the recent development of the highly specific α_2-agonist dexmedetomidine, there has been renewed interest in this class of drug for use in the perioperative period.[2 3 7–9] These drugs offer both analgesia and sedation with little if any impairment of respiratory function—a combination that could be useful in the postoperative or ICU setting.[5] In addition, dexmedetomidine[2] and clonidine (on the basis of this study investigating infusions of duration 1 h) have the interesting property that they allow quick and easy arousal from sedation. This enabled the subjects (and presumably patients) to answer questions and to participate in testing. Clonidine has been investigated extensively for its analgesic and anaesthetic sparing qualities, but its long elimination half-life of 8.5 h[4] makes its use for continuous i.v. sedation and analgesia difficult, and there is no consensus on appropriate dose regimens.

Rat studies have shown MAC (minimum alveolar concentration) reduction in this class of drugs to be mediated by central α_2-adrenoceptors alone, without involvement of opioid and adenosine receptors.[10] MAC reduction from clonidine is reported to be 40% in humans.[11] Because of the incomplete MAC-sparing effects of clonidine, care must be taken when it is used as an adjuvant during anaesthesia, to ensure a depth that is adequate to avoid awareness.

Responses to very high i.v. doses of clonidine have been described. One study in postsurgical patients used 8 µg kg^{-1} i.v. (which produced plasma clonidine concentrations of 2.5 ng ml^{-1}) followed by patient-controlled clonidine analgesia, and found this regimen to be associated with considerable and increasing sedation over the 600 min period of the study.[1] This dose also produced a significant fall in blood pressure (>25 mm Hg). In an effort to avoid unnecessary haemodynamic effects, the present study examined lower doses of clonidine.

Clonidine doses up to 4–5 µg kg^{-1} have been investigated frequently, though primarily for their anaesthetic-sparing effects in the intraoperative period and for their opioid-sparing effects in the postoperative period. Oral premedication with 5 µg kg^{-1} has been used successfully to improve intraoperative haemodynamic stability and reduce anaesthetic[11] and opioid requirements.[2] A pre-emptive dose of 4–5 $\mu g\ kg^{-1}$ i.v. followed by infusion (plasma concentration approx. 1.7 $ng\ ml^{-1}$) has also been shown to have a morphine-sparing effect for postoperative analgesia.[5, 13] Several studies used similar dosing of clonidine to reduce morphine requirements and reported that sedation with clonidine was not greater than that of the morphine control.[5, 6] The present study achieved plasma concentrations above 1.5 $ng\ ml^{-1}$ during the 4 $\mu g\ kg^{-1}\ h^{-1}$ infusion, which was associated with analgesia and good sedation that was easily overcome by calling the patient's name in a normal or loud voice. The lower plasma concentrations studied in this protocol did not result in significant analgesia, but did provide easy arousal from sedation without impairing cognitive function.

A limitation of this research is that only healthy volunteers were studied with short-duration infusions and we cannot be certain that these findings translate to the patient population in pain or stressful settings. However, our findings seem to be consistent with patient studies in which patients received i.v. clonidine during the perioperative period.

The present study attempted to assess the depth of hypnosis using a processed EEG monitor. The BIS monitor provided an objective assessment of sedation and proved to be a sensitive correlate of dose. BIS findings were supported by the subjective, observer-assessed OAA/S measurement, so that bispectral analysis of EEG may be a useful assessment tool when using α_2-agonists. α_2-Agonists behave differently from other sedatives, seemingly producing something closer to sleep, as we recorded BIS numbers in the 30 s in a few volunteers, during which the infusion rate was 4 $\mu g\ kg^{-1}\ h^{-1}$, and yet we were able to awaken them immediately to BIS numbers above 90 to perform tests. During general anaesthesia (or i.v. sedation with common drugs such as propofol and opioid/benzodiazepine combinations), BIS scores as low as this would be taken to indicate deep sedation or hypnosis and immediate waking would not be possible.[14] Consistent with our previous study using dexmedetomidine, a rapid increase in the level of consciousness sufficient to perform neurocognitive tests is a unique characteristic of α_2-agonist sedation.[2]

Clonidine has a low ratio of α_2 to α_1 activity in the rat brain (220:1),[15] and this might result in some α_1-receptor side-effects. In fact, i.v. boluses of clonidine can cause transient hypertension, and both α_2- and α_1-receptor agonism on vascular smooth muscle has been implicated.[16, 17] However, transient hypertension has not been seen in patients undergoing spinal surgery and receiving i.v. clonidine (5 $\mu g\ kg^{-1}$ followed by an infusion).[5] In fact, significant decreases in MAP were noted and were associated with increased cumulative fluid volume in the postoperative period.[5] In the present study, which used young healthy volunteers, cardiovascular changes were small. A recent study in a similar volunteer population with low-dose clonidine supports our findings.[18] These volunteer studies support the hypothesis of De Kock and colleagues that clonidine produces analgesia at doses lower than those required to cause significant hypotension,[13] and extend this hypothesis by demonstrating significant sedation without analgesia when using clonidine at lower doses. However, we cannot rule out the possibility that the presumed lower sympathetic tone in volunteers not in pain from surgery might contribute to the smaller decreases in arterial pressure noted in this protocol.

A limitation of this study is the short (1 h) duration of infusion of clonidine and the possibility that a steady state was not achieved. Although plasma concentrations of clonidine after the 15 min load and at the 60 min time point were identical for each infusion group, the effect site concentration may not have been equilibrated. The two lower infusion rates of clonidine were more likely to have achieved a steady state, based on stable BIS recordings during the last 15 min of the 1 h infusion. However, the 4 $\mu g\ kg^{-1}\ h^{-1}$ infusion resulted in decreasing BIS values (at 45, 50, 55 and 60 min the average BIS was 64, 60, 58 and 56 respectively), suggesting that the effect sites had not achieved steady state.

The respiratory effects of clonidine have been much debated,[19–22] but the consensus appears to be that it is associated with little respiratory depression, and this study would confirm that. α_2-Adrenoceptor agonists, although found throughout the brainstem, are not thought to have a specific role in central respiratory control.[23] One potential respiratory problem with this class of drugs lies in the fact that they dry the mucous membranes. After the 4 $\mu g\ kg^{-1}\ h^{-1}$ dose, volunteers consistently complained of a dry mouth. The drying of secretions suggests there might be a potential for effects on respiratory function through increased mucous viscosity and, consequently, plugging. If this class of drugs is to be used for postoperative sedation, this potential will have to be evaluated.

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Model-based administration of inhalation anaesthesia
1. Developing a system model

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This paper is the first of a series of reports on a system model for the administration of inhalation anaesthesia. We present the development and basic testing of the model. It is a multiple-gas model; it covers fresh-gas flow rates from basal to more than total ventilation and includes an actual, not an idealized, circle-absorber breathing system featuring a standing bellows ventilator. Kinetics of nitrogen, oxygen, carbon dioxide, nitrous oxide, inhaled anaesthetic agents and helium are described. Their partial pressures sum to the total pressure. Ventilation and cardiac output are treated as continuous, not cyclical. The model of the breathing system was empirically matched to the chosen one (a GMS absorber and 7850 ventilator (Datex-Ohmeda)). Predictions for the wash-in of isoflurane and the uptake of desflurane and isoflurane agree well with observed data. The results obtained by continuously checking total gas pressures, calculating mass balances and simulating the measurement of alveolar space by the closed-circuit helium dilution method support the mathematical credibility of the model. It thus merits further exploration.

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We have previously described and validated a system model for closed-circuit inhalation anaesthesia (CCA), focusing our interest on the kinetics of inhaled anaesthetic agents.[1–5] We now wish to extend this model. The extended system model should meet three essential design criteria: (i) all gases present are to be included so that the partial pressures sum to the total pressure; (ii) fresh-gas flows (FGFs) from basal to more than the total ventilation are to be represented; (iii) the anaesthetic breathing system is to be a specific, clinically familiar one with a standing bellows, partitioned into three subsystems. Ventilation and cardiac output are treated as continuous, not cyclical.

Two clinically important purposes of our study are to assist in the automation of CCA and to develop model-based strategies which can be used in clinical practice as rules of thumb to administer inhaled agents.

In this paper, we present the development of the model mainly through the processes of description, mathematical formulation and basic testing. The model of the breathing system is empirically matched to the chosen one. Another paper explores the model in greater detail.[6] The results presented in these two papers have been the basis for the clinical validation and clinical application which remain to be reported in future papers in this series.

Methods

The model is described in non-mathematical terms. Appendices 1–3 contain the mathematical formulation along with the necessary notation. A special-purpose simulation language was used to translate the mathematically formulated model into a computer program (Tutsim 7; Meerman Automation, Neede, The Netherlands). The integration routines used the Euler method with a fixed step size ($\Delta t \leqslant 0.1$ s) [With $\Delta t \leqslant 0.1$ s, simulation was slow. One of the authors (J.L.) is preparing a version of the model using the Simulink and Matlab software (MathWorks, Natick, MA, USA). This simulation environment is also based on the use of building blocks, but, unlike Tutsim, uses a variety of integration routines speeding up the simulations, provides a fully graphical user interface and has widespread use.]

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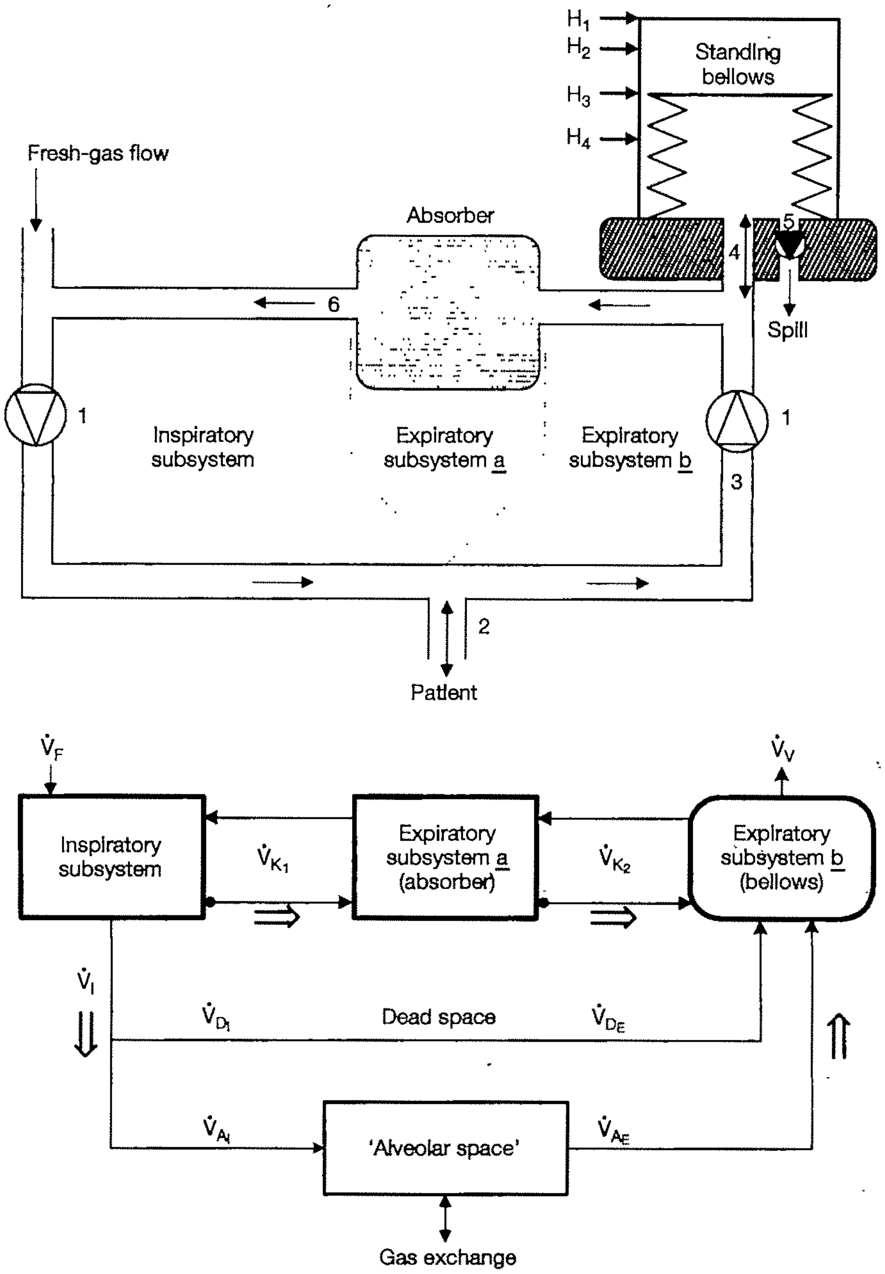

Fig 1 Schematic diagram of anaesthetic breathing system: stylized functional units of the breathing system (top) and their counterparts for the mathematical analysis (bottom). Top: The arrows (→) indicate the direction of the gas flow in the case of rebreathing. 1=one-way valve; 2=Y-piece where the model subject or mock lung was connected; 3 and 4=measuring points where carbon dioxide waveforms were measured in the clinical setting; 5=spill valve; 6=measuring point to detect carbon dioxide when used as a tracer gas (see text); H_1=maximum height of standing bellows in the cage before gas is spilt; H_2=target end-expired height during closed-circuit anaesthesia; H_3 and H_4=actual and end-inspiratory height during a respiratory cycle. During inspiration the spill valve is closed. During expiration, it remains closed until the rising bellows is blocked at the top of its cage (H_1). Pressure then builds up, and the valve opens at a negligible pre-set pressure to spill excess breathing system gases. If fresh gas is added to the breathing system so that the end-expired height of the bellows is maintained below the top (at H_2), no gas is spilt. Bottom: The mathematical notation is elaborated in Appendices 1 and 2. Again the arrows indicate the direction of the gas flow in the case of rebreathing. Gas flows between subsystems ($\dot{V}_{K_1}$ and $\dot{V}_{K_2}$) are either in the direction of rebreathing (→) or in the (opposite) direction of non-rebreathing conditions (●→). The symbol arrows indicate the directions of flow taken as positive in the equations.

Summary of approach

The system model describes the changes in partial gas pressures with time in a subject attached to an anaesthetic breathing system (by 'anaesthetic breathing system', we mean a circle breathing system with carbon dioxide absorption). At the start of each simulation run, the model subject is breathing room air under non-rebreathing conditions. The system model has two major portions: the anaesthetic breathing system and the subject breathing from it. The first has totally new properties. The structure of the subject model differs only slightly from that described fully elsewhere.[1 3 4] Modifications originate from the demands of the new model.

First, to include carbon dioxide and oxygen, the exchange rates of both are defined in terms of age, body mass, height, gender and respiratory exchange ratio. Inspired alveolar ventilation is then calculated as that required to maintain the desired alveolar carbon dioxide partial pressure during air breathing; cardiac output is derived from oxygen requirement and an assumed a–v difference of oxygen content. Second, when absorption of inert soluble gases is considerable, alveolar volume and inspired ventilation are assumed constant. Therefore expired ventilation decreases and this affects the exchange of other gases. Third, by defining three compartments within the breathing system, it is possible to predict the (mean) height of the standing bellows so that the model can assist the automation of CCA using a standing bellows ventilator.

The principle of conservation of mass is applied to describe the transfer of mass for each of the gas species in each of the subsystems of the breathing system, and in the alveolar space. The quantity of gas is expressed in moles. The quantity of a gas may also be described in terms of a volume, expressed in litres, provided the temperature, humidification and pressure of the gas are specified. We assume a state of ambient temperature and pressure, in dry conditions (ATPD) for the gases within the breathing system, and body temperature and pressure, in saturated conditions (BTPS) for those within the alveolar space with appropriate conversion between the two (Appendix 2).

The system model (Figures 1 and 2)

Breathing system

The specific breathing system simulated is the GMS Absorber and the 7850 standing bellows ventilator (Datex-Ohmeda).[7] Figure 1 shows that the breathing system is divided into three functional subsystems: (i) an inspiratory subsystem; (ii) a rigid canister including the absorbent for carbon dioxide; (iii) expiratory tubing and a compressible and collapsible standing bellows. Each subsystem is a chamber accommodating a part of the gas within the circle system, but also communicating with the other subsystems. This configuration implies selective inspiration of fresh gases as well as spilling of fully mixed expired gases. The volume of each of the subsystems was identified from measured data as follows.

Helium dilution was used to measure the internal volume of the complete breathing system including the breathing tubing. The volumes of the tubes were measured by filling them with known volumes of water. The volumes of the canister and the standing bellows were assessed from the exterior. Defining the volume of the inspiratory subsystem was a problem. During expiration, FGF still enters the breathing system while the inspiratory one-way valve is closed (Figure 1). As a consequence, fresh gas must enter expiratory parts of the breathing system and accumulate there until the next inspiratory phase. This assumption was verified first.

A 4 m long sampling capillary of a respiratory mass spectrometer (QP9000; CaSE, Gillingham, UK) was inserted through a home-made inlet (replacing the oxygen analyser) in the inspiratory side of the circle system and moved as far as possible in the direction of the absorber (point 6 in Figure 1). A mock lung (BOC, UK) attached to the Y-piece connector was mechanically ventilated using room air as the fresh gas. Carbon dioxide boluses of a few millilitres, i.e. small enough not to disturb FGF, were injected into the breathing system at the common gas outlet. The presence of fresh gas at point 6 would be revealed by detecting traces of carbon dioxide.

The 'volume' of the inspiratory subsystem was defined while ventilating the mock lung at 12 bpm and an *I:E* ratio of 1:2 with the 7850 ventilator, which is a constant flow rate ventilator. Step changes in the composition of fresh gas from room air (plus the 50 ml min^{-1} safety flow of oxygen) to pure oxygen were performed with fresh-gas flow rates of 7, 3 and 1 litre min^{-1} (ATPD) at a constant total ventilation of 7 litres min^{-1} (ATPD). The step response of oxygen was measured by mass spectrometry, gas being sampled from the Y-piece. The measured response was compared with that predicted by the model. The lung volume and the gas exchange in the model were, properly, reduced to 0.5 litres and zero, respectively. The program was run several times with different settings for the 'volume' of the inspiratory subsystem.

Carbon dioxide concentrations were measured during clinical anaesthesia at three different points: at the Y-piece connector, at the machine end of the expiratory limb (point 3 in Figure 1) and at the point where the gases enter and leave the bellows (point 4 in Figure 1). Electrically operated three-way valves allowed the mass spectrometer to sample gas sequentially from the Y-piece and one of the two other points.

Subject model

The general structure (Figure 2) is, *mutatis mutandis*, similar to that in the previous model.[1 3 4] It is recapitulated in Appendix 3 for the sake of clarity.

Oxygen consumption and carbon dioxide production are considered as being constant. It is assumed that there are no stores for oxygen or carbon dioxide. The alveolar carbon dioxide fraction is determined by the ratio between production and *expired* alveolar ventilation, assuming that all expired carbon dioxide is absorbed or released to the atmosphere. A three-compartment model of shunt, ideal alveoli and dead space is used to model the lungs. The dead-space compartment includes both series and parallel dead space but is treated as all parallel. It is idealized to contain no carbon dioxide.

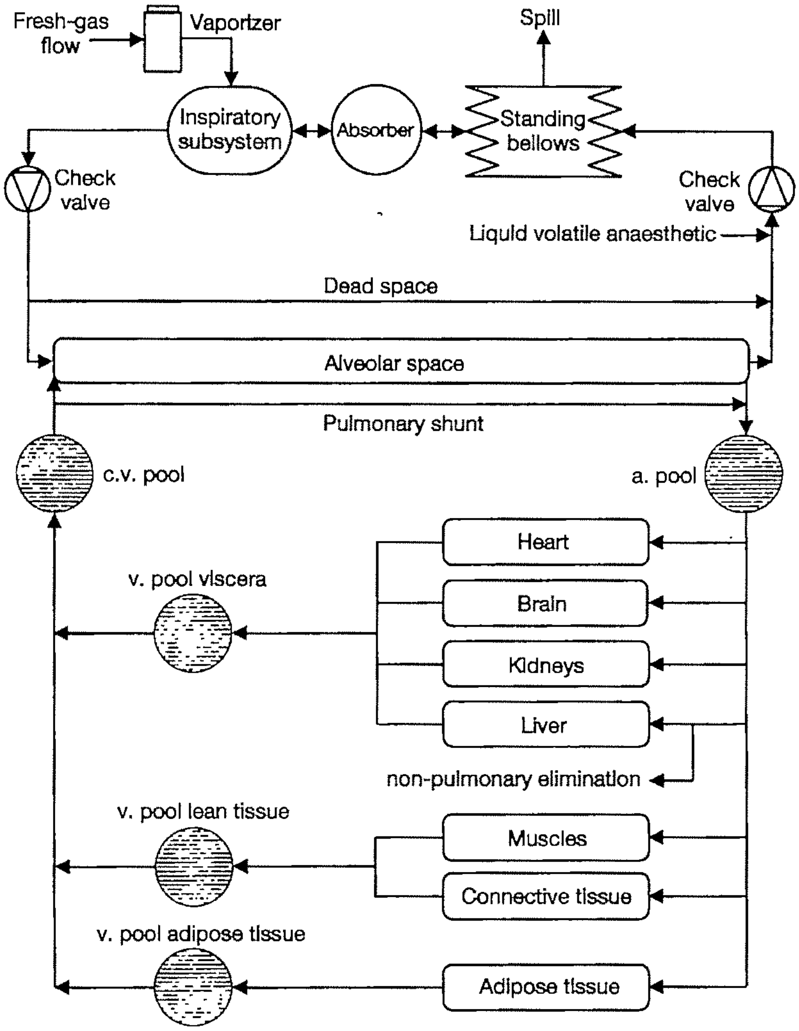

Fig 2 Schematic diagram of complete system model. The anaesthetic circuit portion of the model is shown in more detail in Figure 1. A vaporizer is placed in the FGF line. Liquid volatile anaesthetics are injected into the expiratory limb. The liver compartment includes the liver itself and the complete portal system. The dotted circles represent the blood pools that serve to mimic circulation times in the body (a.=arterial; (c.)v.=(central) venous).[14]

Automation of CCA

An automatic control system was developed to maintain the bellows volume as well as the concentrations of oxygen and anaesthetic agent at a desired level by regulating independently the inflows of oxygen and nitrous oxide (rule-based algorithm shown in reference 6) and agent (proportional-integral-derivative algorithm) into a closed breathing circuit.

Basic testing

Verification

As the model does not use a balance gas, the total gas pressures in the subsystems served as continuous checks on the purely computational validity of the computer predictions. Two explicit simulation tests were also performed to check the mass balances in the breathing system by feeding room air or a sequence of anaesthetic gas mixtures to it. The latter was as follows: after pre-oxygenation (5 min), induction with nitrous oxide 6 litres min^{-1} in oxygen 3 litres min^{-1} (30 min) was followed by administration of 12 vol% (10 min) and 6 vol% (255 min) desflurane in oxygen 0.3 litres min^{-1} and nitrous oxide 0.2 litres min^{-1}. For nitrous oxide and desflurane, we calculated the difference between the accumulated supply and the total of the accumulated spillage, the accumulated amount taken up by the model patient and the amount residing in the breathing system.

To assess the numerical accuracy of the model, we studied its ability to compute predictable events accurately. The volume of the 'alveolar space', V_A (Appendix 2) was computed by simulating the closed-circuit helium dilution method. The model subject, initially breathing air, rebreathed from the closed-circuit spirometer supplied with an oxygen FGF regulated by the rules developed for automated

CCA. After reaching equilibrium, 6 mmol helium was introduced into the system. Zero solubility in lung tissue and in blood was assumed. V_A was found by subtracting the amount of helium (in moles) in the breathing system from the known amount introduced (6×10^{-3} mol) and dividing by the alveolar concentration (mol litre^{-1} BTPS). Thus, expressed in litres BTPS,

$$V_A = \frac{6 \times 10^{-3} - (V_I c_I + V_{Ea} c_{Ea} + V_{Eb} c_{Eb})}{c_A}$$

where c is concentration (mol litre^{-1}) and V is volume (litres); the suffixes I, Ea, Eb and A identify the inspiratory subsystem, absorbers, bellows and alveolar space, respectively.

Initial validation

We mimicked the experimental study of Dwyer and co-workers reporting the wash-in of isoflurane in oxygen under non-rebreathing conditions.[8] A 'dilution factor' d (the fraction of dead-space gas in end-expiratory gas) was deduced from the average arterial and end-expired carbon dioxide tensions: $d=(Pa_{CO_2}-PE'_{CO_2})/Pa_{CO_2}$. Simulated end-expired isoflurane tensions were calculated from the 'ideal' alveolar (PA_{iso}) and dead space (=inspired; PI_{iso}) tensions predicted by our model: $PE'_{iso}=(1-d)\ PA_{iso}+d\ PI_{iso}$. Both definitions are from Landon and co-workers.[9]

A study by Hendrickx and others[10]—who measured the uptake of desflurane or isoflurane during CCA at 1.3 MAC—was emulated. The volume of the anaesthetic circuit in our feedback-controlled system was reduced to match that of their circuit, i.e. 6.3 litres (5.7 litres for the circle system and 0.6 litres for the ventilator).

Results

The volume of the complete breathing system, including the breathing tubing, with a full bellows was 6.6 litres. Small amounts of carbon dioxide injected in the fresh gas were detected at point 6 in Figure 1. At a chosen volume of 2.2 litres for the inspiratory subsystem, acceptable agreement was found between the curves predicted for the alveolar compartment and those measured in the mock lung (Figure 3). Expired gases were partially mixed in the expiratory limb and fully mixed in the bellows (Figure 4). Expiratory subsystem b (Figure 1) was 2.5 litres (1.5 litres bellows, 1 litre expiratory tube, from water-filling) leaving 1.9 litres for expiratory subsystem a, including the volume of the canister.

Computed total gas pressures equalled atmospheric pressure (P_B) at any moment, except when FGF was temporarily zero during CCA. This caused momentary subatmospheric pressures (<30 Pa under P_B or 3 in 10^4) in the various subsystems but not in the bellows (which collapsed). During air breathing, the breathing system was not in a perfect steady state. In 1 h, the total amounts of oxygen, carbon dioxide and nitrogen changed by less than 0.1, 0.1 and –0.01 ppm, respectively, of the amount present in the breathing system plus alveolar space. The absolute differences for nitrous oxide and desflurane, as fractions of their accumulated supplies, were $<1\times10^{-15}$ at any moment of the 5 h simulation run.

The value for V_A calculated from the simulated helium dilution was equal to the set value, i.e. 2.623 litres BTPS (Appendix 2).

Figure 5 compares the end-expired and arterial isoflurane tensions measured in young and elderly adult patients undergoing ventilation to the same arterial carbon dioxide tension with those predicted. The dilution factor was 7.7% for young or 13.5% for elderly patients. Close agreement was obtained: the values were mostly within or very near to the 95% confidence limits.

Figure 6 shows that, in accordance with the study of Hendrickx and others, the target desflurane concentration was reached after $\leqslant 4$ min. Model-predicted cumulative uptakes for desflurane and isoflurane agreed closely with those reported, with some underprediction for time >30 min.

Discussion

The system model incorporates useful new features. Effectively all components of a gas mixture are handled so that the partial pressures sum to the total pressure. Thus, in contrast with the model of Conway,[11] oxygen is not treated as the 'balance gas' in the alveolar space. The model works in moles, albeit partly to avoid unwieldy equations, simulates (mean) bellows volume and lets alveolar ventilation and cardiac output depend on oxygen and carbon dioxide exchange. Some of the features in the present model have appeared in previous models (three-compartment lung, multi-compartment breathing system, circulation time and FGF greater than total ventilation). Other models have included tidal breathing,[12] separate series and parallel dead spaces[13] and even a beat-by-beat circulation.[14]

The breathing system in the model

Our findings show that it is possible to describe the breathing circuit as if it contains effectively three independent compartments (Figures 3 and 4). However, the values chosen for the volumes only hold for an *I*:*E* ratio of 1:2 and a constant flow generator. Our description is compatible with the classification of the GMS absorber breathing system as a C rather than an H arrangement (classifications according to Eger and Ethans[15]) of the circle system.[16] Others have used a two-[17], three-[18] or five-compartment[13] circle. A common (safe) assumption in these arrangements is that alveolar gas is not preferentially exhausted.

Assuming that fresh gas is always completely inhaled does not mimic reality exactly. The model overestimates the

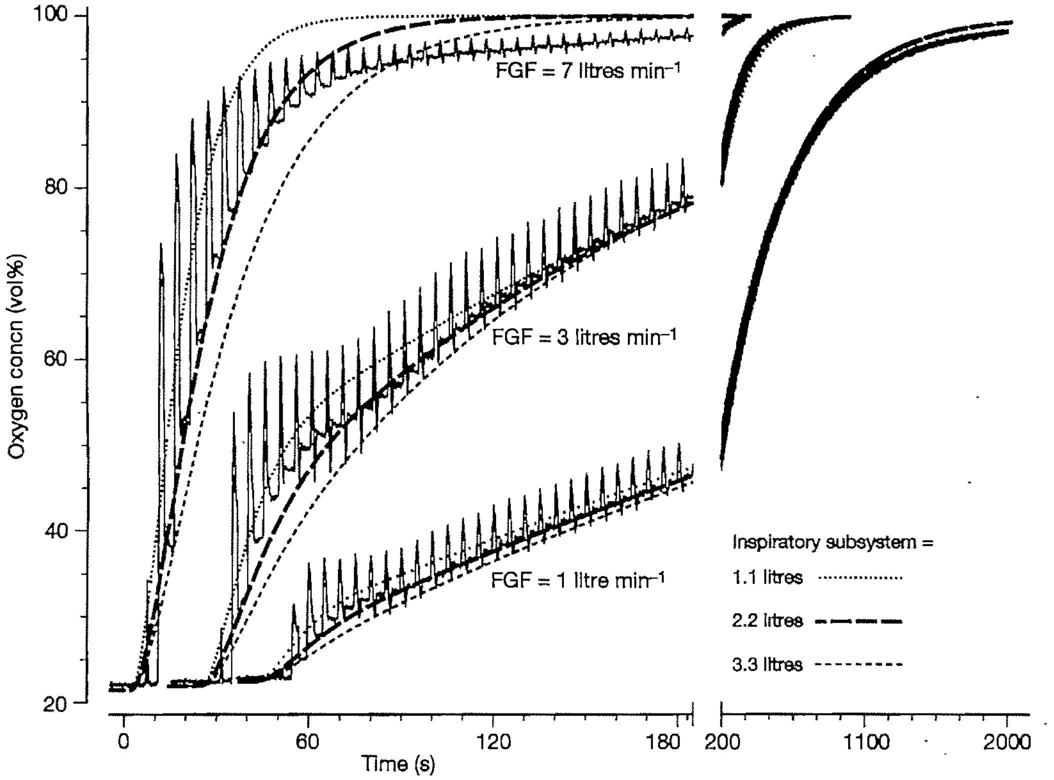

Fig 3 Assessment of the volume of the inspiratory subsystem with a mock lung. Comparison of the step responses in oxygen concentration predicted by the model (discontinuous lines) and those measured (continuous lines) in a mock lung with three FGF settings at a total ventilation of 7 litres min^{-1}. At each setting the volume of the inspiratory subsystem in the model was 1.1, 2.2 or 3.3 litres. The oxygen concentration was measured at the Y-piece connector of the mock lung (point 2 in Figure 1). Oxygen concentrations at the start were slightly greater than in room air because of the ±50 ml min^{-1} safety background flow on the anaesthetic machine. For the sake of clarity only the curves predicted for the alveolar compartment are shown.

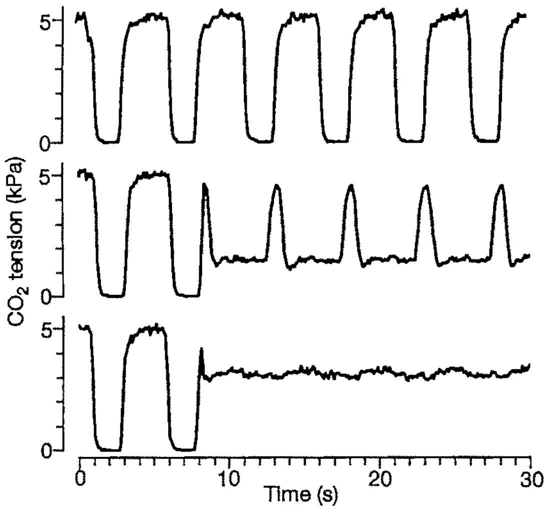

Fig 4 Variation with time of carbon dioxide tension at various points in the anaesthetic breathing system. Top: normal carbon dioxide waveforms (capnograms) obtained at the Y-piece connector. Middle: at t=8 s, sample gas is no longer obtained from the Y-piece but from the machine end of the expiratory limb (point 3 in Figure 1); there the normal capnograms are grossly distorted. Bottom: as a result of mixing, capnograms are completely lost when sampling from the point where the gases enter and leave the bellows (point 4 in Figure 1).

delivery of fresh gases to the mock lung with a high FGF; the reverse is true, to a lesser extent, for FGFs of 3 and 1 litres min^{-1} (Figure 3). Recently, Beams and co-workers have presented a model for the same circle breathing system being used for low-flow anaesthesia (total FGF <1 litre min^{-1}).[18] Their approach differed from ours, in that they assumed complete mixing of the fresh gases with the gases in the absorbers during expiration. They also confined themselves to the case where patient uptake might be assumed to be constant, which allowed a mathematically elegant solution to calculate dosing strategies. Using clinical data for comparison, they found that their model also slightly underestimated the delivery of fresh gases to the patient (with FGF=1 litre min^{-1}).

A 'realistic' representation of the components of the circle system and the FGF in a model is a clinically and experimentally important issue. The ratio of volume and FGF determines the time constant of the processes involved. When changing the settings of rotameters or vaporizers, one time constant is the time required for 63% of the change in concentration to occur in the inspired gas mixture. As our extended model uses a 2.2 litre inspiratory subsystem, a total FGF of 6.6 litres min^{-1} leads to a time constant of 20 s. This is much shorter than the time constant of 60 s which

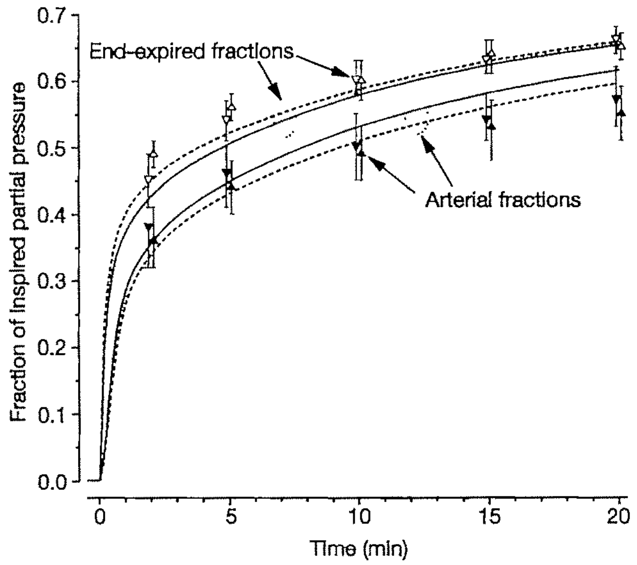

Fig 5 Comparison of end-expired and arterial partial pressures of isoflurane predicted by the model with corresponding measured values and their 95% confidence limits.[8] The predicted (lines) and measured (symbols) values are for young (28 yr; 68 kg) (solid lines; downward-pointing triangles) or elderly (69 yr; 72 kg) (dashed lines; upright triangles) patients. Each of the predicted curves is the average of two curves, one obtained for a male and one for a female subject. For the sake of clarity the downward triangles have been shifted by 0.1 min to the left and the upright triangles to the right.

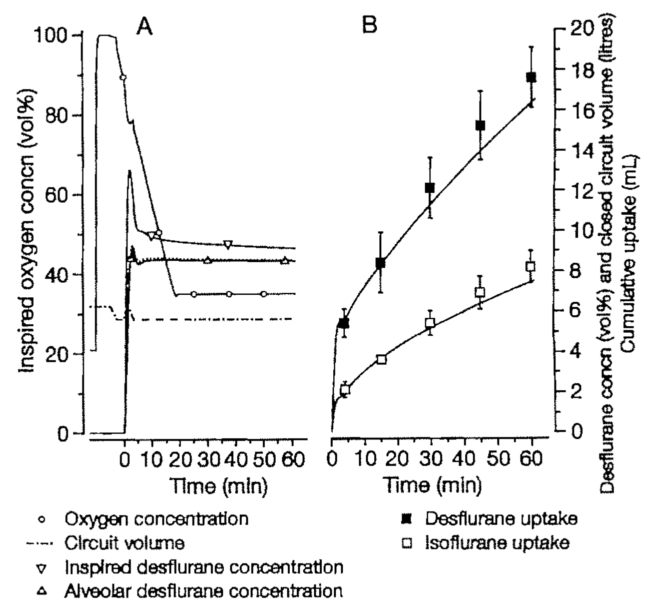

Fig 6 Comparison of the cumulative uptakes of desflurane or isoflurane computed by the system model with those measured by Hendrickx and co-workers.[10] (A) The pattern for the inspired oxygen concentration, the circuit volume and the inspired and alveolar desflurane concentrations are from the simulated desflurane anaesthetic. End-expired values (dotted line) were computed on the assumption that the dilution factor was 7.7% (deduced from the report by Dwyer and others[8] for young patients (Figure 5)). (B) Continuous lines represent computed uptakes. The uptake figures reported by Hendrickx and co-workers[10] for desflurane and isoflurane are given as means±SD. The simulation is for their average 42 yr old female patient of 1.65 m height, and 74 kg (desflurane) or 66 kg (isoflurane) body weight.

would follow from a one-compartment 6.6 litre circle system.

The specific breathing system was selected because: (i) we had gained extensive experience with it;[2–5] (ii) it is the breathing system in current routine use in the operating theatres where clinical validation studies are to be performed; and (iii) the standing bellows enables us to administer CCA. Other circle systems may behave differently; for example, they may be less or more efficient in the usage of fresh gas or the spilling of alveolar gas than the one considered here. Appropriate modules are to be developed for simulating other breathing systems.

In previous papers, we assumed that an increment of liquid anaesthetic agent vaporized, after injection, over a period of 60 s into the one-compartment 6.6 litre closed breathing system. We assumed that the volume of the breathing system did not expand and that volatile anaesthetic could not leave the system.[2–5] The extended model is capable of mimicking the injection in the expiratory part of the system (Figure 2), including the effects on the volume of the standing bellows. Excess volume of gas and vapour, if present, would now be spilt to the scavenging system (Figure 7).

In the clinical environment, gases initially present in the circle system as well as the fresh gas are under ATPD conditions. Moist warm expired gas enters the breathing system and both heat and water vapour are generated during carbon dioxide absorption. Thus the state of gas within the system is between ATPD and BTPS. The exact conditions are not only influenced by the ratio of FGF to total ventilation, but also change as a function of time. A gradient for the temperature and the saturation with water vapour exists along the breathing system.[16 19] These complex and varying conditions would be difficult to simulate in a realistic way. Accuracy of the various calculations is only minimally influenced by our assumption of a state of ATPD for the gases within the breathing system, and BTPS for those within the alveolar space.

Verification

Various procedures were used to verify the system model, i.e. to ascertain its internal mathematical consistency, the numerical accuracy of the computer processor and, especially, the freedom from designer-induced errors. Obviously, errors can occur as a result of entering equations incorrectly into the source code. Errors can also be introduced by the many calculations performed at each time step, e.g. conversions between ATPD, BTPS and standard temperature and pressure, dry (STPD) conditions. The results obtained by continuously checking total pressures, computing mass balances and calculating V_A support the mathematical credibility of the computer model. The

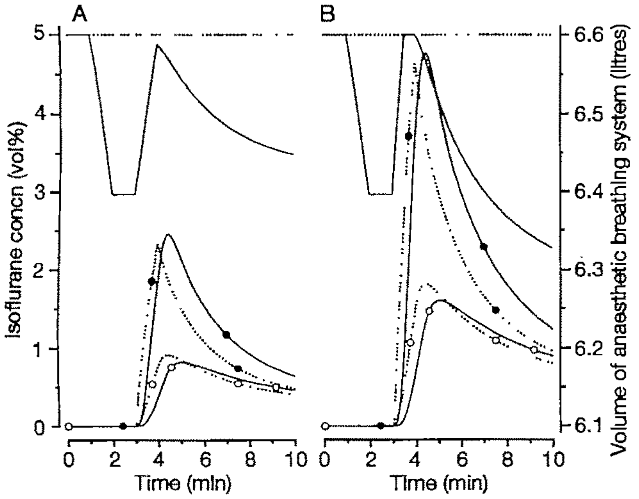

Fig 7 Variation with time of volume of the anaesthetic breathing system and isoflurane concentrations as a result of the injection of 1 ml (A) or 2 ml (B) liquid isoflurane into the 'closed' breathing system (at t=3 min) of the previous[1] (dotted lines) and the new model (continuous lines). (A) Volume of the anaesthetic breathing system (no symbols), inspired (closed symbols) and alveolar (open symbols) isoflurane concentrations. Increments of liquid anaesthetic agent vaporize into the one-compartment 6.6 litre closed breathing system (old model) or in the expiratory part of the system (new model; Figure 2). Breathing system volume remains constant (old model) or varies (new model). The FGF (ATPD)—defined only in the new model—is 9 litres min^{-1} air (0–1 min), zero (1–2 min) and 0.217 litres min^{-1} oxygen thereafter (equal to oxygen uptake expressed at ATPD conditions). This particular sequence was chosen to avoid influences of the exchange of other gases on the kinetics of isoflurane—one source of differences between the old and new model. Cardiac output is 4.84 litres min^{-1} (old model) or 5.35 litres min^{-1} (extended model; Table 2). (B) Symbols, lines and FGF are as on the left. The old model only handles inhaled anaesthetic agents under idealized closed-circuit conditions since it does not have a spill valve. In the new model, but *not* in the old one, excess volume of gases and vapour (equivalent of 0.051 ml liquid isoflurane) is momentarily (3.6–4.2 min) spilt to the scavenging system when the rising bellows reaches the top of its cage (H_1 in Figure 1 and its legend).

helium dilution method indeed relies absolutely upon the total amount of helium that is present remaining constant.

The equation used for measuring V_A is not the conventional one because the subdivision of the circuit into three subsystems is far from the ideal situation where the gaseous contents of the spirometer are fully mixed by a blower.[20]

The results from the mass balances agree with those from Mapleson's most recent model.[13]

Initial validation

To gain confidence in the new model we first sought to mimic studies performed in other institutions. Our own quantitative studies testing the model's performance remain to be reported. The close agreement between the cumulative uptake predicted and that measured[10] (Figure 6) is further corroborated by the very similar observations of Walker, Chakrabarti and Lockwood for desflurane.[21]

'Ideal' alveolar gas cannot be sampled, so it is not uncommon to compare model-based 'ideal' alveolar tensions with measured end-expired tensions of anaesthetic agents[5 10 17 22] or to use the former as an approximation to the latter,[23] partly because of the uncertainty about the difference and partly because the 'ideal' alveolar–end-expired difference is normally quite small for agents with lesser blood solubility. Landon and co-workers reported an ideal alveolar:end-expired ratio of 0.96 (range 0.93–1.00) for isoflurane.[9] The data from the clinical study[8] which we used as comparison for the wash-in of isoflurane made it possible to compute end-expired isoflurane tensions (Figure 5). We believe that this was an acceptable matching of our model to their experimental conditions. The average dilution factor d we used (10.6%) was similar to the average d reported by Landon and colleagues, i.e. 11.58% (range 4.44–23.81%).[9] These d were obtained in different ways: we had to compute d from the average carbon dioxide tensions, whereas Landon and colleagues could calculate d for each individual and report the average. Obviously, the use of d did not affect the comparison for the arterial values. It is noteworthy that one can derive from the same recent study by Landon and others,[9] a value for the wasted ventilation (53%) similar to that chosen in our model (50%) (Appendix 2).

Subject model

The model includes oxygen and carbon dioxide exchange but these, and the derived alveolar ventilation and cardiac output (Appendices 2 and 3), are fixed for a run. There is no representation in this model of oxygen and carbon dioxide transport, and certainly not of the dynamic links between oxygen delivery, oxygen consumption and cardiac output.

In a study that explored the relationship between oxygen uptake and cardiac output, thus reporting simultaneously measured values in the same patients (n=6), Brismar and co-workers reported that, during surgery under halothane anaesthesia, mean (SD) cardiac output was 4.58 (0.38; 95% confidence interval (CI)=4.18–4.98) litres min^{-1} and oxygen uptake 185 (19.3; 95% CI=165–205) ml min^{-1} (STPD).[24] The model predicts for their average 69 yr old female patient a cardiac output of 4.45 litres min^{-1} and an oxygen uptake of 167 ml min^{-1} (STPD). During well-controlled CCA conditions, Couto da Silva, Mapleson and Vickers reported an oxygen consumption of 176 ml min^{-1} (STPD) (no variability reported; core temperature decreased from 36.3°C to 35.8°C),[25] while our model predicts 166 ml min^{-1} (STPD) for their average 45 yr old 67 kg female patient of 1.65 m in height. Thus predicted values for oxygen uptake may slightly underpredict those measured[24 25] because the chosen 20% reduction in metabolic rate—resulting from the anaesthetic state and artificial ventilation—could be too large (Appendix 2).

Table 1 General quantities, symbols, units and remarks; the quantities are listed in alphabetical order of their symbols

Quantity	Symbol	Units	Remarks
Concentration	c	mol litre^{-1}	
Fractional concentration, dry	F		dimensionless
Amount of substance	n	mol	
Mass flow rate	$\dot{n}$	mol s^{-1}	
Pressure	P	kPa	standard sea level atmospheric pressure P_B is 101.325 kPa
Universal gas constant	R	J mol^{-1} K^{-1}	R=8.31430 J mol^{-1} K^{-1}
Temperature	T	K	standard temperature is 273.15 K; room temperature is 295.15 K; body temperature is 310.15 K
Volume	V	litres	gases require definition of conditions (STPD, ATPD, BTPS) (Table 4)
Molar gas volume	V_{mo}	litres STPD mol^{-1}	$V_{mo} = 273.15R/P_B \approx 22.4135$ litres STPD mol^{-1}
Gas flow rate	$\dot{V}$	litres s^{-1}	averaged over a respiratory cycle; requires definition of conditions (STPD, ATPD, BTPS) (Table 4)
Fractional concentration, wet	Φ		dimensionless

Reservations

The many simplifying assumptions that had to be made to arrive at a manageable model have been discussed by many authors.[1] To those already given above, we add: (i) cardiac output and its partitioning do not change; (ii) rotameters and vaporizers exactly deliver gas flows and concentrations as set; (iii) patient temperature is constant at 37°C.

Our results suggest that the extended model has satisfactory accuracy and thus merits further exploration, validation and application in other studies.

Appendix 1: Quantities, symbols and units (Table 1)

This appendix explains the interrelations between various measures of concentration and partial pressure (or tension) of gases and vapours.[26] The new system model is self-checking because a 'balance' gas[11] has not been used in the description of the subsystems. This means that the partial pressures of all gas species present in a subsystem are first calculated and then added to determine the local total gas pressure. As a result, errors are rapidly revealed by checking the total pressure in each of the model's subsystems.

In the mathematical analysis, the suffix S can be A (alveolar space), D (dead space), Ea (expiratory subsystem a), Eb (expiratory subsystem b), F (fresh gas), I (inspiratory subsystem) or V (vented gas, i.e. gas spilled to the scavenging system) (Figures 1 and 2).

Equations relating the quantities listed in Table 1 will be defined first. The equation of state for gas i in a mixture of N ideal gaseous species in subsystem S is:

$$P_{S_i} = RT_S \frac{n_{S_i}}{V_S} \tag{1}$$

where i=1...N for carbon dioxide, oxygen, nitrogen, nitrous oxide, inhaled anaesthetic agent, helium, ..., water vapour; the value of N varies as a function of the gas mixture under consideration, but the order of the first six gases is given and water vapour is assumed to be the N^{th} gas species.

The concentration of gas i, expressed in mol litre^{-1}, is:

$$c_{S_i} = \frac{n_{S_i}}{V_S} \tag{2}$$

Summing the partial pressures of all gas species yields the total pressure:

$$P_s = \sum_{i=1}^{N} P_{S_i} \tag{3}$$

Summing the masses of all gas species yields the total mass:

$$n_S = \sum_{i=1}^{N} n_{s_i} \tag{4}$$

The fractional concentration of component i in a wet, ideal gas mixture is:

$$\Phi_{s_i} = \frac{P_{S_i}}{P_S} \tag{5}$$

If the total pressure P_S in the subsystem equals 101.325 kPa (1 atm), then the partial pressure P_{S_i} of gas i (in kPa) is approximately equal to Φ_{S_i} expressed as a percentage of atmospheric pressure. For example, if the alveolar partial pressure of oxygen is 30 kPa, then the wet fractional concentration is approximately 30%.

The fractional concentration of gas i in a dry, ideal gas mixture is given as ($i \neq N$):

$$F_{S_i} = \frac{P_{S_i}}{P_S - P_{S_{H_2O}}} \tag{6}$$

Combining equations (5) and (6) yields ($i \neq N$):

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Table 2 Specification of the model patient used for all simulations: an anaesthetized 40 yr old man of 70 kg body mass and 1.80 m in height. Room (ambient) temperature is 295.15 K. The values for which equation number(s) are not given are chosen values. A calculated value is first given in the coherent units used in the required equation, then in alternative units. FRC=functional residual capacity. Conversion factors between STPD, ATPD and BTPS conditions are given in Table 4

	Values in equations		**Equation number**	**Rounded value in other units**
	Chosen	**Calculated**		
Metabolism				
Body temperature (K)	310.15			
Respiratory exchange ratio	0.82			
Oxygen requirement (litres s^{-1} STPD)		4.19000×10^{-3}	(22)	0.252 litres min^{-1} STPD
Oxygen consumption (mol s^{-1})		149.455×10^{-6}	(23)	0.201 litres min^{-1} STPD
Carbon dioxide production (mol s^{-1})		122.553×10^{-6}	(23)	0.165 litres min^{-1} STPD
Ventilation				
Ventilatory frequency (min^{-1})	10			
Alveolar partial pressure of carbon dioxide (kPa)	5.33000			
Ventilation wasted by dead space effect (%)	50			
Inspiratory alveolar ventilation (litres s^{-1} ATPD)		53.5832×10^{-3}	(24)	3.601 litres min^{-1} BTPS
Inspiratory dead space ventilation (litres s^{-1} ATPD)		53.5832×10^{-3}	(26)	3.601 litres min^{-1} BTPS
Inspiratory total ventilation (litres s^{-1} ATPD)		107.1664×10^{-3}	(25)	7.202 litres min^{-1} BTPS
Tidal volume (litres ATPD)		642.9984×10^{-3}	after (27)	0.720 litres BTPS
Lungs				
Arteriovenous difference in oxygen content (litres STPD $litre^{-1}$ of blood)	0.047			
Alveolar partial pressure of water (kPa)		6.27181	(8)	
FRC (litres BTPS)		2.263	(28)	
Alveolar space (FRC+half tidal volume) (litres BTPS)		2.623	(27)	
Circulation				
Pulmonary shunt fraction	0.05			
Cardiac output (litres s^{-1})		89.0907×10^{-3}	(43)	5.345 litres min^{-1}

$$\frac{P\mathrm{s}_i}{P\mathrm{s}} = \Phi\mathrm{s}_i = F\mathrm{s}_i\left(1 - \frac{P\mathrm{s}_{\mathrm{H_2O}}}{P\mathrm{s}}\right) \tag{7}$$

Values for $P\mathrm{s}_{\mathrm{H_2O}}$ in saturated gas mixtures (283.15–311.15 K) may be represented by:[27]

$$P\mathrm{s}_{\mathrm{H_2O}} = 0.1333\Big[9.993 - 0.3952(T - 273.15) + 0.03775(T - 273.15)^2\Big] \tag{8}$$

Hence, at body temperature (T=310.15 K), $P\mathrm{A}_{\mathrm{H_2O}}$=6.27181 kPa. Thus fractional concentrations of permanent gases in wet gas mixtures at 310.15 K and 101.325 kPa have approximately 6.2% lower values than fractional concentrations in dry gas mixtures (equation (7)).

Appendix 2: Model of the breathing system and the lung

Values for partial pressures to start a simulation run are obtained in two steps.

Step 1

Initial values before running the model are chosen or calculated. The breathing system is filled with dry room air, which is assumed to contain 20.90 and 79.10 vol% of oxygen and nitrogen, respectively, at sea level atmospheric pressure, $P\mathrm{B}$. The model patient is specified in Table 2. The alveoli contain a saturated gas mixture in which the oxygen tension is derived—using the ideal alveolar air equation—from the oxygen tension in moist inspired gas, the chosen initial alveolar carbon dioxide tension (Tables 2 and 3), the chosen value for respiratory exchange ratio R_{n} (Table 2) and the initial value for the oxygen tension in the inspiratory subsystem (Table 3).[28] Hence, assuming air breathing:

$$P\mathrm{A}_{\mathrm{O_2}} = 0.209(P\mathrm{B} - P\mathrm{A}_{\mathrm{H_2O}}) - \frac{P\mathrm{A}_{\mathrm{CO_2}}}{R_{\mathrm{n}}} + \frac{P\mathrm{I}_{\mathrm{O_2}}}{P\mathrm{B}}\left(\frac{P\mathrm{A}_{\mathrm{CO_2}}}{R_{\mathrm{n}}} - P\mathrm{A}_{\mathrm{CO_2}}\right) \tag{9}$$

Initially alveolar nitrogen is the balance gas. Initial values are summarised in Table 3.

Step 2

Near 'steady state' values are then obtained by running the model on air breathing for 1 h. It is assumed that 0.15 litres s^{-1} of air (ATPD) is flowing into the breathing system. This is more than the total ventilation (Table 2) and, therefore, in combination with the chosen values for the subject (Table 2), determines the starting values for the partial pressures of the respiratory gases in the various locations (Table 3). The

Table 3 Selected quantities, symbols and values for the subsystems of the anaesthetic breathing system (Figure 1) and the alveoli. Initial values are those before running the model (for details see Appendix 2). 'Steady state' values result from running the model on air breathing for 1 h under non-rebreathing conditions. In turn, the 'steady state' values were the initial values for all simulations. The initial and 'steady state' values for all partial pressures of nitrous oxide, helium and anaesthetic agent are zero and therefore not mentioned in the table. The volumes for the subsystems are expressed in litres ATPD except for the alveoli which are expressed in litres BTPS

	Inspiratory subsystem			**Alveoli**		
Quantity	**Symbol**	**Initial value**	**Steady state value**	**Symbol**	**Initial value**	**Steady state value**
Carbon dioxide partial pressure (kPa)		0.0	0.0	$P\mathrm{A}_{\mathrm{CO_2}}$	5.33000	5.33000
Nitrogen partial pressure (kPa)	$P\mathrm{I}_{\mathrm{N_2}}$	80.1481	80.1481	$P\mathrm{A}_{\mathrm{N_2}}$	76.1125	76.1125
Oxygen partial pressure (kPa)	$P\mathrm{I}_{\mathrm{O_2}}$	21.1769	21.1769	$P\mathrm{A}_{\mathrm{O_2}}$	13.6106	13.6106
Water vapour partial pressure (kPa)	$P\mathrm{I}_{\mathrm{H_2O}}$	0.0	0.0	$P\mathrm{A}_{\mathrm{H_2O}}$	6.27181	6.27181
Temperature (K)	$T\mathrm{I}$	295.15	295.15	$T\mathrm{A}$	310.15	310.15
Volume (litres)	$V\mathrm{I}$	2.2	2.2	$V\mathrm{A}$	2.623	2.623

	Bellows (expiratory subsystem b)			**Absorbers (expiratory subsystem a)**		
Quantity	**Symbol**	**Initial value**	**Steady state value**	**Symbol**	**Initial value**	**Steady state value**
Carbon dioxide partial pressure (kPa)	$P\mathrm{Eb}_{\mathrm{CO_2}}$	0.0	2.01368	$P\mathrm{Ea}_{\mathrm{CO_2}}$	0.0	0.0
Nitrogen partial pressure (kPa)	$P\mathrm{Eb}_{\mathrm{N_2}}$	80.1481	80.4977	$P\mathrm{Ea}_{\mathrm{N_2}}$	80.1481	80.1481
Oxygen partial pressure (kPa)	$P\mathrm{Eb}_{\mathrm{O_2}}$	21.1769	18.8136	$P\mathrm{Ea}_{\mathrm{O_2}}$	21.1769	21.1769
Water vapour partial pressure (kPa)	$P\mathrm{Eb}_{\mathrm{H_2O}}$	0.0	0.0	$P\mathrm{Ea}_{\mathrm{H_2O}}$	0.0	0.0
Temperature (K)	$T\mathrm{Eb}$	295.15	295.15	$T\mathrm{Ea}$	295.15	295.15
Volume (litres)	$V\mathrm{Eb}$	2.50	2.50	$V\mathrm{Ea}$	1.90	1.90

convention is that the breathing system is at room temperature and the patient at body temperature (Table 1). Accordingly, the gases occupying and leaving the breathing system are defined at ATPD, while those occupying and leaving the alveoli are defined at BTPS.

Gas flows in the breathing system (Figure 1)

Fresh-gas flow

The fresh gas can consist of a mixture (ATPD) of air, oxygen, nitrous oxide, a volatile anaesthetic agent and an insoluble gas such as helium. The flows of oxygen, nitrogen and nitrous oxide constitute the carrier gas mixture (or 'background flow') to which the vapour of a volatile anaesthetic agent is added. The vapour flow rate (litres s^{-1} ATPD) supplied to the breathing system is given as:

$$\dot{V}\mathrm{F}_{\mathrm{agent}} = (\dot{V}\mathrm{F}_{\mathrm{O_2}} + \dot{V}\mathrm{F}_{\mathrm{N_2}} + \dot{V}\mathrm{F}_{\mathrm{N_2O}}) \times \frac{F_{\mathrm{vap}}}{1 - F_{\mathrm{vap}}} \qquad (10)$$

where F_{vap} is the fractional concentration delivered from the vaporizer. Thus we augment the carrier gas flow to allow for vaporized agent, and the FGF rate is the sum of the flow rates of all gases and vapours entering the inspiratory subsystem from outside the breathing system (no carbon dioxide or water vapour):

$$\dot{V}\mathrm{F} = \sum_{i=2}^{N-1} \dot{V}\mathrm{F}_i \qquad (11)$$

Ventilation is assumed to be continuous; therefore, if inspiratory ventilation exceeds FGF, inspiratory ventilation comprises the FGF supplemented by rebreathed gas. Expired gases are fully mixed in the bellows (Figure 4).

Gas flows between subsystems of breathing system

If rebreathing exists, i.e. if $\dot{V}\mathrm{F} < \dot{V}\mathrm{I}$, gas flows between subsystems (see Figure 1 and its caption for sign convention) are given by:

$$\dot{V}\mathrm{K}_2 = -(\dot{V}\mathrm{A_E}K_{\mathrm{BSAD}} + \dot{V}\mathrm{D_E} - \dot{V}\mathrm{V} + \dot{V}_{\mathrm{Eb}\rightarrow\mathrm{Ea}}) \qquad (12)$$

and

$$\dot{V}\mathrm{K}_1 = -\,(\dot{V}\mathrm{A_E}K_{\mathrm{BSAD}} + \dot{V}\mathrm{D_E} - \dot{V}\mathrm{V} - \dot{V}\mathrm{CO_2}, \text{absorbed} + \dot{V}_{\mathrm{Ea}\rightarrow\mathrm{I}}) \qquad (13)$$

where $\dot{V}\mathrm{A_E}$, $\dot{V}\mathrm{D_E}$ and $\dot{V}_{\mathrm{V}}$ are the expired alveolar and dead space ventilation and the vented flow, respectively (Figure 1), K is a conversion factor between the different conditions of the gas mixtures (Table 4) and $\dot{V}\mathrm{CO_2}$, absorbed is the carbon dioxide scrubbed in the absorber (litres s^{-1} ATPD;

Table 4 K_{XXYY} is a factor that converts gas volumes from a source condition, XX, to a target condition, YY, where BS=body temperature (310.15 K) and pressure, saturated (water vapour pressure is 6.27181 kPa); AD=ambient temperature (295.15 K) and pressure, dry; SD=standard temperature (273.15 K) and pressure, dry. Derivation of conversion factors is as given by Nunn[43]

Factor	Approximate value
K_{ADBS}	1.12016
K_{ADSD}	0.92546
K_{BSAD}	0.89273
K_{SDAD}	1.08054
K_{SDBS}	1.21038

equation (41)). Expired dead-space ventilation is in litres s^{-1} ATPD (see before equation (33)). Gas outflow from the absorber ($\dot{V}_{\mathrm{K}_1}$) is less than the inflow ($\dot{V}_{\mathrm{K}_2}$) as a result of carbon dioxide scrubbing.

The terms with a prime are included in equations (12) and (13) *only* for those conditions where FGF is smaller than uptake or even zero, e.g. at the start of CCA. Rebreathed gas plus fresh gas then fail to cover inspired ventilation. As a result, sub-atmospheric pressure develops in the inspiratory subsystem and the absorber. The pressure in the bellows, however, remains atmospheric as its volume can shrink (equation (36)).

As the breathing system is a system of communicating chambers, a passage of flow of gas from the bellows through the absorber to the inspiratory subsystem prevents sub-atmospheric pressure from developing by letting:

$$\dot{V}'_{\mathrm{Eb}\rightarrow\mathrm{Ea}}=\frac{P_{\mathrm{B}}-P_{\mathrm{Ea}}}{\left[\dfrac{P_{\mathrm{B}}\Delta t}{1.25V_{\mathrm{Ea}}}\right]} \tag{14}$$

$$\dot{V}'_{\mathrm{Ea}\rightarrow\mathrm{I}}=\frac{P_{\mathrm{B}}-P_{\mathrm{I}}}{\left[\dfrac{P_{\mathrm{B}}\Delta t}{1.25V_{\mathrm{I}}}\right]} \tag{15}$$

where Δt is the time step used in the integration algorithm. The denominator in the right-hand side (RHS) of equations (14) and (15) has the dimensions of resistance (kPa s litre^{-1}). Each RHS was first theoretically defined, then adjusted by trial and error (manipulating the small dimensionless factor 1.25) to minimize the duration of the period of subatmospheric pressure. Simpler definitions could be used in a later version.

If no rebreathing exists, i.e. if $\dot{V}_{\mathrm{F}}>\dot{V}_{\mathrm{I}}$, excess gas escapes from the inspiratory subsystem via the absorbers and the standing bellows to the scavenging system. It follows, simply, that (see Figure 1 and its caption for sign convention):

$$\dot{V}_{\mathrm{K}_1}=\dot{V}_{\mathrm{F}}-\dot{V}_{\mathrm{I}} \tag{16}$$

and

$$\dot{V}_{\mathrm{K}_2}=\dot{V}_{\mathrm{F}}-\dot{V}_{\mathrm{I}} \tag{17}$$

Inspiratory subsystem

The differential equations derived from the principle of conservation of mass describe the changes in the number of moles of gas i (where i >1, because we assume that all carbon dioxide is absorbed or vented, and $i \neq N$ as ATPD conditions prevail) with time as:

$$\frac{\mathrm{d}n_{\mathrm{I}_i}}{\mathrm{d}t}=\dot{V}_{\mathrm{F}_i}c_{\mathrm{F}_i}-\dot{V}_{\mathrm{I}}c_{\mathrm{I}_i}-\dot{V}_{\mathrm{K}_1}c_{\mathrm{I}_i}\qquad \text{if } \dot{V}_{\mathrm{K}_1}>0 \tag{18}$$

$$\frac{\mathrm{d}n_{\mathrm{I}_i}}{\mathrm{d}t}=\dot{V}_{\mathrm{F}_i}c_{\mathrm{F}_i}-\dot{V}_{\mathrm{I}}c_{\mathrm{I}_i}-\dot{V}_{\mathrm{K}_1}c_{\mathrm{Ba}_i}\qquad \text{if } \dot{V}_{\mathrm{K}_1}<0 \tag{19}$$

Note that concentration c is in mol litre^{-1} (Table 1). An initial value for n_{I_i} is obtained from the initial value of P_{I_i} (Table 3) and a specific, rearranged form of equation (1):

$$n_{\mathrm{I}_i}=\frac{P_{\mathrm{I}_i}V_{\mathrm{I}}}{RT_{\mathrm{I}}} \tag{20}$$

Since the number of moles of each gas species occupies the constant volume of the inspiratory subsystem, subsequent partial pressures and concentrations of component i are given at any moment by equations (1) and (2), respectively, with S=I The total pressure is given by equation (3) and the inspired fractional concentrations by equations (5) and (6), with S=I.

Model lung

The model lung consists of gas exchange space ('alveolar space' containing 'ideal' alveolar gas), functional dead space and lung tissue. The disappearance of a gas from the alveoli is dictated not only by the amount of gas that exchanges with blood, but also by that dissolving in lung tissue. The amount dissolved at any moment is the product of the alveolar concentration, the lung tissue volume V_{lt} and the lung tissue/gas partition coefficient λ_{lt}.[29] Gases introduced into the alveoli equilibrate in <1.5 s with the pulmonary parenchymal tissue.[30] The rate of uptake by lung tissue of gas i at time t, expressed in litres s^{-1} BTPS, is defined ($i \neq N$; V_{mo} is molar gas volume (Table 1)) as:

$$\dot{V}_{\mathrm{lt}_i} = V_{\mathrm{lt}} \times \lambda_{\mathrm{lt}_i} \times \frac{c_{\mathrm{A}_i}(t) - c_{\mathrm{A}_i}(t - \Delta t)}{\Delta t} V_{\mathrm{mo}} K_{\mathrm{SDBS}} \tag{21}$$

Alveolar space and alveolar ventilation

Using the definition of Dubois and Dubois[31] for body surface area (m^2), and combining the data of Boothby, Berkson, and Dunn[32 33] for metabolic rate with that of Zuntz and Shumburg[34] for energy production, we define the typical oxygen requirement, expressed in litres s^{-1} STPD, as a function of body mass (M in kg), height (H in cm), age (A in years), gender (male: δ=44.24, γ=0.142; female: δ=39, γ=0.1), and R_n (=0.82 for a ratio of 39% carbohydrates to 61% fat in the diet):

$$\dot{V}\mathrm{O}_2 = 0.007184 \times M^{0.425} \times H^{0.725} \times \frac{\delta - \gamma A}{[4.686 + 1.232(R_n - 0.707)] \times 3600} \tag{22}$$

where the factor 3600 converts hours into seconds. Using a factor 0.8 to correct the typical oxygen requirement for the depressant effects of general anaesthesia and artificial ventilation, the oxygen consumption and the carbon dioxide production, both expressed in mol s^{-1}, are given as:

$$\dot{n}_{\mathrm{O}_2} = \frac{0.8\,\dot{V}\mathrm{O}_2}{V_{\mathrm{mo}}} \qquad \dot{n}_{\mathrm{CO}_2} = \frac{0.8\,R_n \dot{V}\mathrm{O}_2}{V_{\mathrm{mo}}} \tag{23}$$

Consequently, the flow, expressed in litres s^{-1} ATPD, that leaves the inspiratory subsystem and enters the alveolar space, i.e. the inspiratory alveolar ventilation necessary to maintain a chosen alveolar partial pressure of carbon dioxide (Table 2) during the initial period of air breathing, is given as:

$$\dot{V}_{\mathrm{A}_\mathrm{I}} = \frac{\dot{n}_{\mathrm{CO}_2} RT_{\mathrm{body}}}{P_{\mathrm{A}_{\mathrm{CO}_2}}} K_{\mathrm{BSAD}} + (\dot{n}_{\mathrm{O}_2} - \dot{n}_{\mathrm{CO}_2}) V_{\mathrm{mo}} K_{\mathrm{SDAD}} \tag{24}$$

Inspired ventilation is held constant, whereas expired ventilation will vary as gases other than oxygen and carbon dioxide are involved in gas exchange in the lungs.

Inspiratory and dead space ventilation; functional dead space

If we assume that x% of the total inspiratory ventilation is 'wasted' as dead-space ventilation, the inspiratory ventilation (ATPD) is

$$\dot{V}_\mathrm{I} = \frac{100}{(100 - x)} \dot{V}_{\mathrm{A}_\mathrm{I}} \tag{25}$$

and the inspiratory dead space ventilation (ATPD) is then, by definition:

$$\dot{V}_{\mathrm{D}_\mathrm{I}} = \dot{V}_\mathrm{I} - \dot{V}_{\mathrm{A}_\mathrm{I}} \tag{26}$$

Reported values of x are in the range 30–70.[9 11 35 36] The apparatus dead space of the tracheal tube and its connections must be added to the physiological dead space (i.e. anatomical plus alveolar dead space) for the purpose of calculating wasted ventilation. The functional dead space (sum of the apparatus, anatomical and alveolar dead spaces) then amounts to a mean of 50% of the tidal volume at tidal volumes of >350 ml.[37] If a facemask is used, the functional dead space increases to about two-thirds of the tidal volume.[37] The value of x is a numerically important factor for the rate of wash-in of gases when using FGFs greater than alveolar ventilation. During CCA, however, the value of x has minimal impact.[38] We chose a value of 50.

Although the model is non-cyclic in nature, a definition of a tidal volume (V_T) is needed to calculate the volume of the 'alveolar space' (litres BTPS) as:

$$V\mathrm{A} = V_{\mathrm{FRC}} + 0.5 V_\mathrm{T} K_{\mathrm{ADBS}} \tag{27}$$

where V_T is the quotient of the inspiratory minute volume (litres min^{-1} ATPD) and the chosen breathing frequency (10 min^{-1}; Table 2), and V_{FRC} is the functional residual capacity which depends on height (H in m), age (A in years) and gender:[39]

$$V_{\mathrm{FRC}} = 0.65(2.340H + 0.009A - 1.090) \text{ for men}$$
$$V_{\mathrm{FRC}} = 0.65(2.240H + 0.001A - 1.000) \text{ for women} \tag{28}$$

The factor 0.65 reflects the impact of the supine position and the anaesthetized state.[1]

'Uptake'

The total mass flow rate across the alveolo-capillary membrane (mol s^{-1}) is:

$$\dot{n}_{\mathrm{AC}} = \sum_{i=1}^{N-1} \dot{n}_i \tag{29}$$

Here $\dot{n}_{\mathrm{O}_2}$ and $\dot{n}_{\mathrm{CO}_2}$(equation (23)) must have opposite signs. The convention is that $\dot{n}_{\mathrm{O}_2}$ is nominally positive (oxygen uptake by the blood) and $\dot{n}_{\mathrm{CO}_2}$ negative (carbon dioxide entering the alveolar space from the blood). $\dot{n}_i$ for any other gas i is defined in equation (42).

Expiratory alveolar ventilation

The model assumes that the 'alveolar space' has a constant volume; thus expiratory alveolar ventilation (litres s^{-1} BTPS) is given as:

$$\dot{V}_{A_E} = \dot{V}_{A_I} K_{ADBS} - \left(\dot{n}_{AC} V_{mo} K_{SDBS} + \sum_{i=1}^{N-1} \dot{V}_{lt_i} \right) \quad (30)$$

Alveolar space: gas composition

The change with time of the number of moles of gas i in the 'alveolar space' plus lung tissue is given as ($i \neq N$; $\dot{n}_i$ is the molar uptake of gas i):

$$\frac{dn_{A_i}}{dt} = \dot{V}_{A_I} c_{I_i} - \dot{V}_{A_E} c_{A_i} - \dot{n}_i \quad (31)$$

The sign convention for oxygen and carbon dioxide 'uptake' applies as after equation (29). As with the inspiratory subsystem (equation (20)), an initial value for n_{A_i} is obtained from the initial value of P_{A_i} (Table 3) and a specific, rearranged form of equation (1). However, here it is necessary to take account of the gas required to equilibrate lung tissue with alveolar gas:

$$n_{A_i} = (V_A + V_{lt} \lambda_{lt_i}) \frac{P_{A_i}}{R T_A} \quad (32)$$

Subsequently, partial pressures, concentrations, etc. can be obtained as described after equation (20).

Dead space and dead-space ventilation

These are treated conventionally, as in other models with 'continuous' ventilation. Any dead space is parallel dead space and there are no kinetics whatsoever for filling and emptying (as in tidal ventilation).[23] Dead-space effect is treated as a short cut for inspiratory ventilation. Expired dead-space ventilation is thus expressed in litres s^{-1} ATPD and is equal to inspired dead-space ventilation (equation (26)):

$$\dot{V}_{D_E} = \dot{V}_{D_I} \quad (33)$$

Dead-space concentrations are equal to inspiratory concentrations (defined after equation (20)):

$$c_{D_i} = c_{I_i} \quad (34)$$

Expiratory subsystem b

The change of the number of moles of gas i in this subsystem with time is given as ($i \neq N$):

$$\frac{dn_{Eb_i}}{dt} = \dot{V}_{D_E} c_{D_i} + \dot{V}_{A_E} c_{A_i} + \dot{V}_{K_2} \check{c}_i - \dot{n}_{V_i} \quad (35)$$

where $\dot{n}_{V_i}$ is the rate of venting of substance i (mol s^{-1}; equation (38)). If $\dot{V}_{K_2} > 0$, then $\check{c}_i = c_{Ea_i}$; if $\dot{V}_{K_2} < 0$, $\check{c}_i = c_{Eb_i}$. Injecting liquid anaesthetic agent is simulated by adding its equivalent (mol s^{-1}) to the RHS of equation (35) (i=5) over a period of 60 s. An initial value for n_{Eb_i} is obtained as described before equation (20); but the way in which subsequent values of n_{Eb_i} are processed is different because the volume of this subsystem can vary between 1 litre (bellows empty) and 2.5 litres (bellows full). Therefore the volume (ATPD) that the contained gas molecules occupy (or would occupy) is:

$$V_{Eb_{gases}} = V_{mo} K_{SDAD} \sum_{i=1}^{N-1} n_{Eb_i} \quad (36)$$

If $V_{Eb_{gases}}$ >2.5 litres, the pressure P_{Eb} increases above atmospheric pressure. The increase is limited, however, by releasing gas to the atmosphere through the spill valve (strictly, spilling should occur when $V_{Eb_{gases}}$>2.5 litres–$0.5 V_T$ as the 'movable' parts of the system are, mathematically, at their mean positions):

$$\dot{V}_V = \dot{V}_F + \dot{V}_{liq} - \left[\dot{n}_{AC} V_{mo} K_{SDAD} + \sum_{i=1}^{N-1} \dot{V}_{lt_i} K_{BSAD} + \dot{V}_{CO_2, \text{absorbed}} \right] \quad (37)$$

where $\dot{V}_V$ is the vented flow (litres s^{-1} ATPD) and $\dot{V}_{liq}$ is the flow of gaseous anaesthetic (litres s^{-1} ATPD) that results from the vaporization[40] of an injected liquid compound. On the other hand, if $V_{Eb_{gases}} \leq 2.5$ litres, the subsystem is not pressurized, P_{Eb} is necessarily equal to ambient pressure P_B, no gas is spilled, and $\dot{V}_V$=0. In both conditions, partial pressures, concentrations, and the total gas pressure P_{Eb} are obtained as described after equation (20) except that, in calculating P_{Eb_i} from equation (1), V_S must be set equal to $V_{Eb_{gases}}$ if this is <2.5 litres, but to 2.5 litres if $V_{Eb_{gases}}$ is greater.

The vented amount of substance i is given as ($i \neq N$):

$$\dot{n}_{V_i} = \dot{V}_V \, c_{Eb_i} \quad (38)$$

Expiratory subsystem a

The change of the number of moles of gas i in the absorber with time is given as ($i \neq N$):

Table 5 Partition coefficients for nitrogen,[44] nitrous oxide,[45] desflurane and isoflurane.[45] The blood/gas partition coefficient of desflurane is from Lockwood, Sapsed-Byrne and Smith.[46] Accordingly, tissue/blood partition coefficients for desflurane were obtained by dividing reported[47] tissue/gas partition coefficients by 0.52. The lung tissue/blood partition coefficients for desflurane and isoflurane were calculated from their lung/gas coefficients (as reported by Mapleson[13]) and the appropriate blood/gas coefficients as listed. Lung tissue/gas partition coefficients for carbon dioxide, oxygen and nitrogen were calculated from data given by Grant,[48] on the assumption[29] that they are numerically the same as their solubility coefficients in water at 310.15 K, i.e. 0.622, 0.026, and 0.014, respectively

	Nitrogen	Nitrous oxide	Desflurane	Isoflurane
Blood/gas	0.0147	0.47	0.52	1.50
Tissue/blood				
Lung tissue	1.0	1.0	1.30	1.1
Kidney	1.0	0.87	0.77	1.3
Heart	1.0	1.13	1.04	1.5
Brain	1.0	1.06	1.04	2.4
Liver	1.0	0.93	1.06	2.3
Muscle	1.0	0.86	1.81	1.5
Connective tissue	1.0	0.8	1.40	2.0
Adipose tissue	3.6	3.0	23.08	63.0

Table 6 Default values for the body compartments (Figure 2). Volumes are expressed as fractions of the body mass (M). The remainder is total blood volume (=0.07M) (Table 7). The blood flows through the compartments are expressed as fractions of the cardiac output. Values are data given by Lowe and Ernst.[49] The liver compartment includes the liver itself and the whole portal system

Compartment	Volume	Blood flow
Lung tissue	0.0080	–
Kidney	0.0040	0.250
Heart	0.0040	0.050
Brain	0.0210	0.160
Liver	0.0570	0.300
Muscle	0.4260	0.130
Connective tissue	0.2600	0.060
Adipose tissue	0.1500	0.050

Table 7 Default values for the blood pools (Figure 2). Volumes are expressed as fractions of the body mass (M). Total blood volume (V_{bl}=0.07M) is partitioned into arterial blood volume ($V_{bl,a}$) and venous blood volume ($V_{bl,v}$). The latter constitutes the various venous blood pools. Values are adapted from data of Mapleson[14] and Davis and Mapleson.[50]

Blood pool	Partitioning	Volume
$V_{bl,a}$	$0.2V_{bl}$	0.014
$V_{bl,v}$	$0.8V_{bl}$	
Adipose tissue venous pool	$0.111V_{bl,v}$	0.006216
Central venous pool	$0.126V_{bl,v}$	0.007056
Lean tissue venous pool	$0.364V_{bl,v}$	0.020384
Viscera venous pool	$0.399V_{bl,v}$	0.022344

$$\frac{dn_{Ea_i}}{dt} = \dot{V}_{K_1}\tilde{c}_i - \dot{V}_{K_2}\check{c}_i \tag{39}$$

If $\dot{V}_{K_1}$>0, then $\tilde{c}_i$=c_{I_i}; if $\dot{V}_{K_1}$<0, $\tilde{c}_i$=c_{Ea_i}. If $\dot{V}_{K_2}$>0, then $\check{c}_i$=c_{Ea_i}; if $\dot{V}_{K_2}$<0, $\check{c}_i$=c_{Eb_i}. As with the inspiratory subsystem (equation (20)), an initial value for n_{Ea_i} is obtained from the initial value of P_{Ea_i} (Table 3) and a specific, rearranged form of equation (1). Subsequently, partial pressures, concentrations, etc. can be obtained as described after equation (20). As carbon dioxide entering the absorber is completely scrubbed, its tension is set equal to zero and does not contribute to local total pressure. Nevertheless, the amount $n_{Ea_{CO_2}}$ can be calculated, i.e. accumulated indefinitely, as the moles are there in chemical combination. This amount is used for defining $\dot{V}_{CO_2,\,absorbed}$ (used in equations (13) and (37)), which, in the case of rebreathing, is theoretically given in litres s^{-1} ATPD by:

$$\dot{V}CO_2, \text{absorbed theor} = -\dot{V}K_2 c_{Eb_{CO_2}} V_{mo} K_{SDAD} \tag{40}$$

The sign change results from the convention that $\dot{V}K_2$ is negative in the case of rebreathing.

This definition, when entered into the source code, causes 'algebraic loops' between variables in the model, thus making it impossible to run the simulation. Such loops occur when one or more variables on the RHS of an equation depend—via simple algebraic calculations—on the left hand side, either directly, or by one or more loops. For example, in equation (40), $\dot{V}K_2$ involves $\dot{V}v$ (equation (12)) which, in turn involves $\dot{V}CO_{2,\,absorbed}$; (equation (37)). As no carbon dioxide leaves the absorber, it is possible to define at time t:

$$\dot{V}_{CO_2,\,absorbed} = \frac{\left(n_{Ea_{CO_2}}(t) - n_{Ea_{CO_2}}(t-\Delta t)\right)V_{mo}K_{SDAD} + C}{\Delta t} \tag{41}$$

where C is the difference between theoretical (equation (40)) and practical (equation (41)) accumulated amounts of absorbed carbon dioxide. C thus corrects any deviation of the latter from the former. The initial values for the accumulated values are zero because it is assumed that all simulations start with air breathing under non-rebreathing conditions (Table 3). Obviously, under non-rebreathing conditions, $\dot{V}CO_{2,\,absorbed}$=0.

Appendix 3: Model of the circulation and the body tissues

The model of the circulation and the body tissues is the one that has been described in detail in previous papers and references cited therein.[1 3 4] For the sake of clarity, new data in Tables 5–7 are accompanied by a recapitulation of already published material.

Defining the mass flow rate across the alveolo-capillary membrane (see above) forms the mathematical link between the model of the breathing system and lung on the one hand, and that of circulation and body tissues on the other hand. At this stage, there is no submodel for the transport of oxygen and carbon dioxide.

Oxygen uptake and carbon dioxide excretion are defined in equation (23) and are not subject to the same definition of mass flow rate across the alveolo-capillary membrane as other gases which obey (i=3...(N–1)):

$$\dot{n}_i = \dot{Q}(1 - f_s)(\lambda_{B/G}, \Phi A_i - C\overline{v}_i)\frac{K_{BSSD}}{V_{mo}} \tag{42}$$

where $\dot{Q}$ is the cardiac output (litres s^{-1}), f_s is the shunt fraction (Table 2), $\lambda_{B/G}$ is the blood/gas partition coefficient, ΦA is the wet alveolar fractional concentration, and $C\overline{v}$ is the fractional concentration in mixed venous blood, respectively ($C\overline{v}$ belongs to the old model[1] and thus conforms with its notation). Cardiac output in the extended model is given by:

$$\dot{Q} = \frac{\dot{V}O_2}{c_{(a-\bar{v})_{O_2}}} \tag{43}$$

i.e. the ratio of oxygen requirement and arterio–venous difference in oxygen content reported by Paulus (Table 2).[41] In fact the oxygen requirement is reduced by a factor of 0.8 after the calculation of cardiac output (in accordance with Lockwood and White in the printed manual of the computer program Narkup[42]), to allow for the observed depressant effects of general anaesthesia and artificial ventilation (equation (23)).

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Model-based administration of inhalation anaesthesia.
2. Exploring the system model

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We explored our model by displaying its new capabilities, testing its sensitivity to variations in input data and illustrating its use. Its multiple-gas character allows simulation of the mechanisms governing concentration and second gas effects. Simulating the volume of a standing bellows makes it possible to test algorithms for automated closed-circuit anaesthesia. Using desflurane, the model's sensitivity to changes in blood/gas partition coefficient (range 0.42–0.576), cardiac output and minute ventilation was analysed. The model was very sensitive to changes in blood solubility; other results agreed with those reported previously. An alveolar isoflurane tension of 1% atm was rapidly attained and maintained, even using 0.5 litres min^{-1} of fresh gas, when isoflurane was 'co-administered' through a vaporizer set to 3.5 vol% and a single aliquot (1.25 ml liquid) injected into the expiratory limb. As a result of its credibility and capabilities, the model is to be tested in the clinical setting.

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We have described the development of a physiological system model for the kinetics of respiratory and inert gases, including the potent inhalational anaesthetic agents.[1] It incorporates a multi-compartment model of the circulation and body tissues, a three-compartment lung and a three-compartment anaesthetic breathing system (when referring to an anaesthetic breathing system, we imply a circle breathing system with carbon dioxide absorption). Circulation and ventilation are treated as continuous processes.

Here we explore the new model in more detail so as to confirm its credibility before it is applied in the clinical setting. Sets of specific circumstances are created and simulated to: (i) display the new capabilities of the model; (ii) test its sensitivity to variations in input data; and (iii) illustrate the use of the model.

Methods

Except where otherwise stated, input data to the model were those described in our previous paper.[1] Features of the model patient are outlined in Table 1.

Displaying the capabilities of the model

Multiple-gas character

The model subject breathed air (79.1 vol% nitrogen and 20.9 vol% oxygen) from the anaesthetic breathing system, followed by a mixture of 79.1 or 39.1 vol% nitrous oxide, 20.9 vol% oxygen and balance nitrogen. Total fresh gas flow (FGF) was 9 litres min^{-1} (ATPD), which was more than total ventilation (Table 1).

Variety of FGF

A desflurane anaesthetic was emulated using the variation in FGF encountered during clinical practice.

Simulation of bellows volume

A replenishment technique to automate closed-circuit anaesthesia (CCA) was simulated, i.e. the nitrous oxide and oxygen removed by a subject from the closed breathing system were replaced. A control algorithm based on simple decision rules was designed to add oxygen at a rate necessary to maintain a constant oxygen concentration, and nitrous oxide to maintain a constant bellows volume. Shortages in nitrous oxide and oxygen were assessed by

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Table 1 Basic characteristics of the model patient used for all simulations (an anaesthetized 40 yr old man of 70 kg body mass and 1.80 m in height). For a full specification see reference 1. Gas volumes and gas flow rates may be expressed at ATPD (ambient temperature (295.15 K) and pressure, dry), BTPS (body temperature (310.15 K) and pressure, saturated) or STPD conditions (standard temperature (273.15 K) and pressure, dry); to convert a value, multiply it by 1.08054 (to convert STPD to ATPD) or 0.89273 (to convert BTPS to ATPD)

Metabolism	
Oxygen consumption (litres min^{-1})	0.201 (STPD), 0.217 (ATPD)
Respiratory exchange ratio	0.82
Carbon dioxide production (litres min^{-1})	0.165 (STPD), 0.178 (ATPD)
Ventilation	
Alveolar partial pressure of carbon dioxide (kPa)	5.33
Inspiratory alveolar ventilation (litres min^{-1})	3.601 (BTPS), 3.215 (ATPD)
Inspiratory total ventilation (litres min^{-1})	7.202 (BTPS), 6.430 (ATPD)
Tidal volume (litres)	0.720 (BTPS), 0.643 (ATPD)
Lungs	
Functional residual capacity (FRC) (litres)	2.263 (BTPS)
Alveolar space (FRC + half tidal volume) (litres)	2.623 (BTPS)
Circulation	
Pulmonary shunt fraction	0.05
Cardiac output (litres min^{-1})	5.345

calculating the volume of the standing bellows and the oxygen concentration therein. Feedback-controlled CCA began after pre-oxygenation and a period of high FGF (Table 2). A clinically important question to answer was: is it possible to build a stable control system if the shortages are only known at 10 s intervals? Such an interval reflects a realistic time window that is required in practice to detect the volume of the moving bellows.

Sensitivity analysis

Using desflurane, we examined the sensitivity of the model to changes in blood/gas partition coefficient, cardiac output and minute ventilation. Essentially, 12 vol% desflurane was administered for 5 min and 6 vol% thereafter in 0.5 litres min^{-1} each of nitrous oxide and oxygen (Table 2).

Blood/gas partition coefficient

The values chosen were: 0.42, 0.45, 0.48, 0.52, 0.548 and 0.576. Two scenarios were simulated. First, the tissue/gas partition coefficients were kept constant at values that are the products of the basic values in the model for the blood/gas (0.52) and tissue/blood partition coefficients (see reference [1], Table 5). For the second (less likely) scenario, the tissue/blood partition coefficients were kept constant (see reference [1], Table 5).

Cardiac output and ventilation

Simulations were performed with the cardiac output set at its baseline default value (5.345 litres min^{-1}) and at values 50% lower and 50% higher than normal. The cardiac output values other than default were obtained in two different ways. First, cardiac output was modified on its own, i.e. without any concomitant changes in other physiological

Table 2 Sequences of FGF (ATPD) and desflurane or isoflurane concentration leaving the vaporizer in various simulations. The sequences started after an initial period of 60 min air breathing under non-rebreathing conditions; auto=automated flow regulation

Period	Automated CCA		Sensitivity analysis			Isoflurane rapid induction with initial high flow			Isoflurane rapid induction with initial liquid injection		
(min)	FGF oxygen (litres min^{-1})	FGF nitrous oxide (litres min^{-1})	FGF oxygen (litres min^{-1})	FGF nitrous oxide (litres min^{-1})	Desflurane (%)	FGF oxygen (litres min^{-1})	FGF nitrous oxide (litres min^{-1})	Isoflurane (%)	FGF oxygen (litres min^{-1})	FGF nitrous oxide (litres min^{-1})	Isoflurane (%)
−8 to −5	9	0	9 or 12	0	0	9	0	0	9	0	0
−5 to 0	3	6	3 or 4	6 or 8	0	3	6	0	3	6	0
0–1	3	6	0.5	0.5	12	2.5	5.0	3.5	0.3	0.2	3.5
1–5	3	6	0.5	0.5	12	0.5	1.0	3.5	0.3	0.2	3.5
5–12	3	6	0.5	0.5	6	0.4	0.6	2.0	0.3	0.2	3.5
>12	auto	auto	0.5	0.5	6	0.4	0.6	2.0	0.3	0.2	3.5

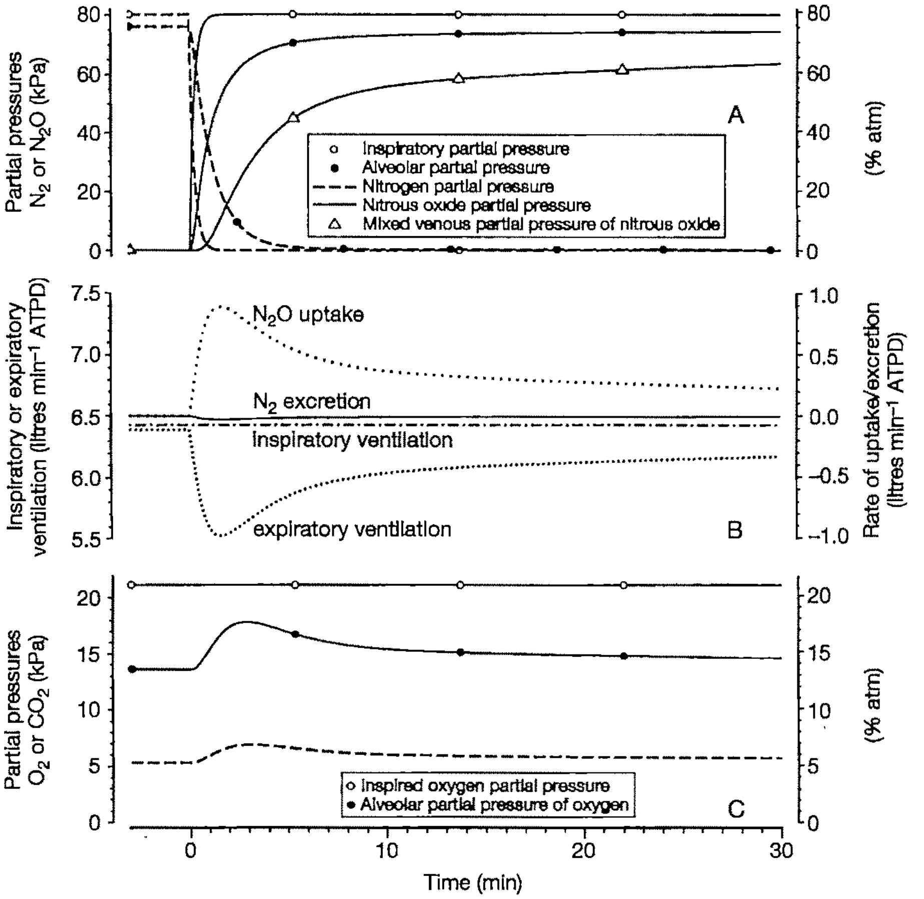

Fig 1 Simulation of the mechanisms governing concentration and second gas effects. At time zero, the inspired gas mixture is abruptly changed from air, which is composed of 79.1 vol% nitrogen and 20.9 vol% oxygen, to a mixture of 79.1 vol% nitrous oxide and 20.9 vol% oxygen. (A) Course of the inspiratory and alveolar partial pressures for nitrogen and nitrous oxide. The subject is denitrogenated as the induction with nitrous oxide proceeds. The mixed-venous partial pressure of nitrous oxide starts to increase after a lag time arising from successive equilibrations with blood pools and tissue compartments in the model (see reference 1, Figure 2). (B) Before zero time, the expiratory ventilation is marginally smaller than the inspiratory ventilation because the respiratory exchange ratio is 0.82. There is a net uptake of large volumes of gas as a result of the exchange between the key gases nitrous oxide and nitrogen. The maximum gas exchange occurs after about 1.5 min, i.e. just after the mixed-venous partial pressure of nitrous oxide starts to increase. The inspired ventilation is held constant, whereas the expiratory ventilation decreases. (C) As a result, in spite of the constant inspired oxygen partial pressure, the alveolar partial pressure of oxygen increases after the onset of the nitrous oxide inhalation. The same is true for carbon dioxide. However, the increase in alveolar carbon dioxide tension is probably exaggerated (see text). ATPD, ambient temperature pressure and dry conditions.

variables, and the variation of the alveolar desflurane tension with time was studied. Second, the change in cardiac output was assumed to be the response to a change in oxygen requirement of the tissues. In view of the ensuing carbon dioxide production, the respiratory minute volume was adjusted to maintain the default target $P\text{A}_{\text{CO}_2}$ (5.33 kPa) (see reference [1], Appendix 2). The variations of the alveolar oxygen, nitrous oxide and desflurane tensions with time were studied.

Use of the model

Clinical purposes

We addressed the clinically important issue of how to achieve 'rapid induction' with minimum usage of a potent inhalational anaesthetic agent, in this case isoflurane. Two different dosing strategies that would be simple to implement clinically were investigated theoretically. The first was a sequence of a high initial FGF at a high inspired isoflurane tension followed by lower flows (Table 2). In the second, we simulated the combined use of a single bolus of liquid isoflurane injected into the expiratory limb of the circle system (see reference [1], Figure 2) and a vaporizer during minimal-flow anaesthesia, i.e. nitrous oxide 0.2 litres min^{-1} in oxygen 0.3 litres min^{-1} (Table 2). Both scenarios had been optimized so that they would increase as quickly as practicable the alveolar isoflurane tension to 1 ± 0.1% atm and maintain it for ≥20 min.

Research and development

We studied how the behaviour of the control system for CCA would be affected by 1% noise disturbing the oxygen signal.

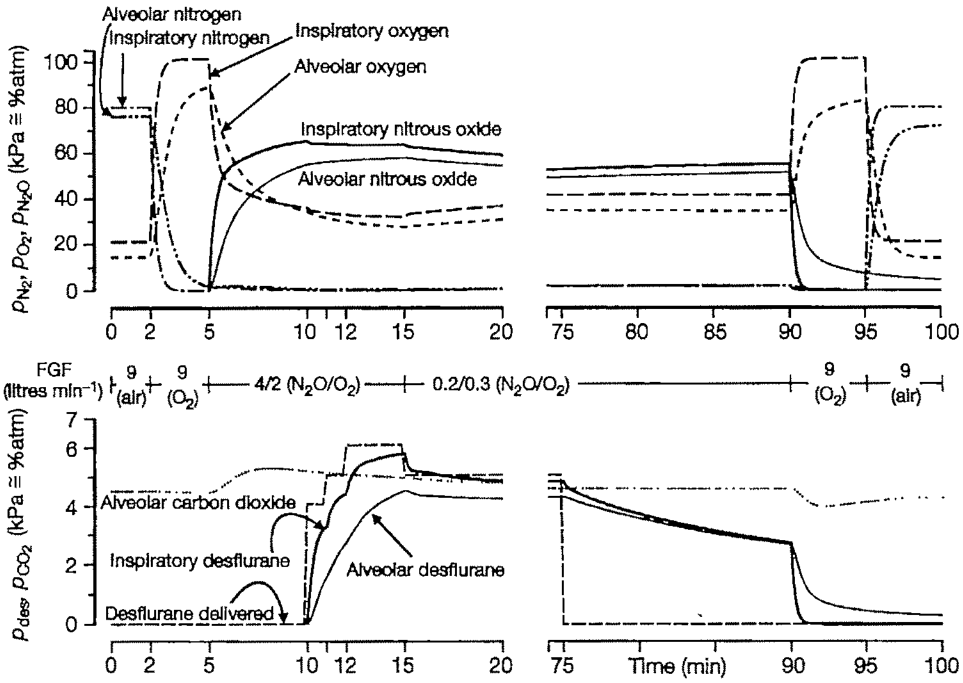

Fig 2 Simulated desflurane anaesthesia. Variation with time of the partial pressures for nitrogen (P_{N_2}), oxygen (P_{O_2}), nitrous oxide (P_{N_2O}), desflurane (P_{des}) and carbon dioxide (P_{CO_2}). The FGFs indicated in the figure do not include the desflurane vapour and are expressed at ATPD. The increase in alveolar carbon dioxide tension is explained in Figure 1 and the reverse effect on carbon dioxide tension can be seen at wash-out. %atm=per centage of atmospheric pressure.

Results

Displaying the capabilities of the model

Multiple-gas character

After the sudden introduction of 79.1% nitrous oxide in the breathing mixture, nitrogen is exchanged for the more soluble nitrous oxide (Figure 1A). Large volumes of nitrous oxide are transferred from alveoli to blood and removed by solution in lung tissue, whereas relatively small volumes of nitrogen are excreted. Since the inspired ventilation and alveolar volume are held constant, the expired ventilation decreases by the amount of the net uptake of gas molecules (Figure 1B). Consequently, there is an increase in the partial pressures of all gases (except nitrogen) present in the alveoli. As this increase depends on the net uptake, the alveolar nitrous oxide fractional concentration (F_A) approaches its inspired fractional concentration (F_I) more quickly when the latter is greater (concentration effect). The difference in F_A/F_I at 3 min is 0.081 for 79.1% compared with 39.1% inspired nitrous oxide. The alveolar oxygen tension increases from 13.61 to 17.86 kPa, despite its constant inspiratory tension, and carbon dioxide tension increases from 5.33 to 6.93 kPa (Figure 1C).

Variety of FGF

The various epochs of a typical desflurane anaesthesia show the wide variety of FGF handled by the model (Figure 2). The initial conditions reflect those of air breathing. The pre-oxygenation (and denitrogenation) process then begins. Since the breathing system is not pre-filled with oxygen, it takes about 1 min for the inspiratory oxygen tension to reach the intended value. Denitrogenation is 95% complete within 3 min.

Administration of 4, 5 and 6 vol% desflurane in an FGF of 6 litres min^{-1} (ATPD; 10–15 min) rapidly achieves the desired alveolar tension. The inspiratory tension does not attain the delivered tension because there is some rebreathing. The chosen FGF is indeed smaller than the minute ventilation of 7.60 litres min^{-1} (ATPD) required to attain the initial target alveolar carbon dioxide tension of 4.50 kPa. Reduction of FGF to 0.5 litres min^{-1}, to which 5% desflurane is added, yields virtually constant desflurane tensions in the period 15–75 min. Nitrous oxide and oxygen partial pressures evolve as dictated by the ratio of the delivery and the uptake of each of the two substances. Ending the delivery of desflurane without increasing FGF causes its tensions to decrease slowly (75–90 min). Nitrous oxide and desflurane are washed out with oxygen (90–95 min). After 5 min of air breathing, oxygen and nitrogen are not far from resuming their initial partial pressures.

Bellows volume

The rules designed to regulate FGF are shown in Figure 3. Figure 4 (left) shows the simulated behaviour of the rule-based control system in the absence of noise. At the start of CCA, oxygen FGF first stops until the bellows volume drops below its target, then reaches oxygen uptake within 2 min. After the change in set point for the oxygen concentration, oxygen inflow first decreases, then again tracks oxygen

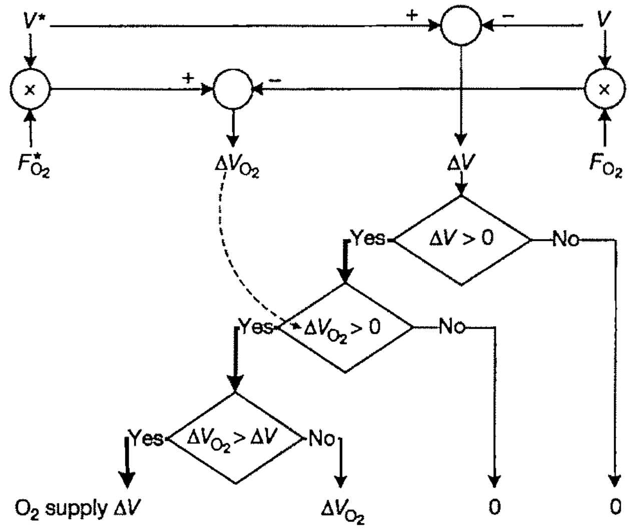

Fig 3 Rules for the automated supply of oxygen and nitrous oxide into the closed breathing system. Subtracting the actual volume (V) of the bellows from its target value (V^*) yields a difference ΔV. If there is no volume shortage in the bellows ($\Delta V \leq 0$), no gases can be added. If there is volume shortage, indicated by a positive ΔV, the supply of fresh gases depends on ΔV_{O_2}. The latter is obtained by subtracting the actual volume of oxygen present in the bellows from the target volume of oxygen (F_{O_2}=actual oxygen fractional concentration in the bellows; $F^*_{O_2}$=set point oxygen fractional concentration). ΔV_{O_2} can be positive, zero (oxygen volume is sufficient within the too small volume of the bellows) or negative. The supply of nitrous oxide is optional and equals the difference between ΔV and the calculated oxygen supply. The thick arrows relate to a numerical example. Suppose the bellows volume is smaller than its target and there is also a shortage of oxygen: e.g. ΔV=0.1 litre and ΔV_{O_2}=0.2 litre. Because ΔV_{O_2} exceeds the shortage of the bellows volume, 0.1 litre of oxygen, but no nitrous oxide, must be supplied to the closed circuit.

uptake. The mean (SD) undershoot of the bellows volume is 53.4 (2.3) ml (13–28 min). For the oxygen concentration the undershoot is 0.46 (0.04) % atm (13–20 min and 21–28 min). Stable conditions are obtained, even though information on the actual volume of the bellows is sampled only once per 10 s. The right-hand half of Figure 4 shows the effect of 1% noise in oxygen measurement.

Sensitivity analysis

The value chosen for the blood/gas partition coefficient has considerable impact on the speed of build-up of desflurane in the alveoli (Figure 5). When tissue/gas partition coefficients are kept constant, concentrations are in the range 4.72–5.21% at 20 min, and the slowest wash-in curve intersects the 5% atm line 16 min later than the fastest curve. On the assumption of constant tissue/blood partition coefficients, the range is 4.67–5.32%, and the difference in time is 21 min.

When *only* the cardiac output was changed, to 50% greater or 50% less than normal, the rate of build up of alveolar desflurane tension was decreased or increased, respectively. The average percentage differences between wash-in curves were −9 (1) % and +13 (1) %, respectively.

Figure 6, depicts the more complex situation where, from the start of the simulation, cardiac output and minute ventilation have been adjusted to the oxygen requirement and carbon dioxide production, respectively.

For time < 0, the FGF is 12 litres min^{-1} (ATPD; nitrous oxide:oxygen 2:1; Table 2) to guarantee non-rebreathing conditions even with increased ventilation. The oxygen tensions decline from the high values obtained through the preceding pre-oxygenation. Nitrous oxide tensions rapidly increase to the tension in the fresh gas. The rate of increase is slowest for the case with concomitant halving of cardiac output and ventilation (closed circles).

For time >0, low-flow conditions prevail (0.5 litres min^{-1} each of oxygen and nitrous oxide). The greater the oxygen uptake (as well as cardiac output and ventilation), the greater the nitrous oxide tensions; the reverse is true for oxygen tensions. All nitrous oxide curves tend to rise after approximately 30 min, whereas all oxygen curves do the reverse. There is little spread in the three curves for desflurane. It appears that the effects of changes in ventilation cancel somewhat the effects of alterations in cardiac output. Concomitantly halving cardiac output and ventilation results in an initial average percentage difference for desflurane of about +7%, falling to less than +2% before 10 min (Figure 6). The difference curve is close to zero for time >20 min, i.e. approximately +1 and −1% at 30 and 60 min, respectively (Figure 6).

Uses of the model

Clinical purposes

The first dosing strategy (Table 2) causes the alveolar isoflurane tension to reach the target at approximately 1 min and to remain within the target window (1±0.1)% atm) thereafter, except for a tiny overshoot at 5 min (Figure 7; open squares). The success of the second regimen (Table 2) depends on the injection of 1.25 ml liquid isoflurane into the expiratory limb of the breathing system. This regimen causes the isoflurane tension to reach the target at 1.5 min with a small overshoot to 1.2% atm, then to drop a little below 1% atm, and to recover to the target. Without the 'priming dose', the target value would not be attained in the first 20 min (Figure 7). The accumulated usage of liquid isoflurane (and nitrous oxide gas) was 4.0 or 3.1 ml (18 or 4 litres) for the first or second dosing schedule, respectively.

Research and development

Figure 4 (right) shows that the presence of noise in the oxygen signal does not alter the behaviour of the bellows, but the inflow of oxygen is chaotic around oxygen uptake.

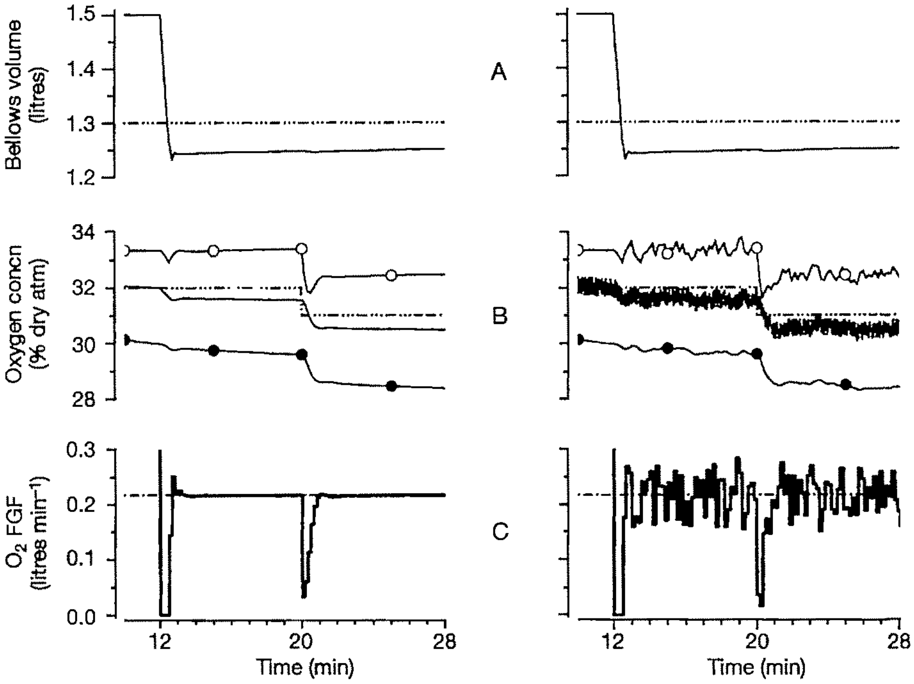

Fig 4 Simulated behaviour of the rule-based system controlling the volume of a standing bellows and the oxygen concentration in the presence of a noise-free signal (left) and a noisy oxygen signal (right). The input to the circle system is as in Table 2. Left: (A) The bellows volume drops from its maximum volume (1.5 litres) after the start of automated CCA, then stabilizes below its target value (– · · · –). (B) The oxygen concentrations are the inspired (open circles), alveolar (closed circles) and bellows (no symbols) concentrations. Bellows oxygen concentration and bellows volume are the two input signals to the rule-based control system (Figure 3). The set point for the oxygen concentration is 32% until 20 min and 31% thereafter. (C) Oxygen FGF rapidly tracks down the oxygen uptake (0.217 litres min^{-1} ATPD; Table 1) (– ● –). The 'steps' in the FGF result from the adjustments in oxygen supply which can be made only at 10 s intervals. FGFs are calculated by dividing the volume shortages (litres ATPD) obtained from the flow chart (Figure 3) by 0.125 min. Right: Labelling of the curves is the same as on the left. As a result of the noisy signal of bellows oxygen concentration, oxygen FGF does not track oxygen uptake properly.

Discussion

The new system model meets the essential criteria that were the basis of its development.[1] The model handles FGFs from basal to more than total ventilation. It describes all gases present in an anaesthetic breathing system with a standing bellows. Simulating the bellows volume is a unique feature.

Displaying the capabilities

Multiple-gas character

The uptake of large volumes of nitrous oxide may be associated with one or more of the following: an increase in inspired ventilation, a decrease in expired ventilation or a shrinkage in lung volume. The latter may be important during breath-holding manoeuvres.[2] The three factors were analysed by Korman and Mapleson in a search for a comprehensive and improved explanation of the concentration and second gas effects.[3] Their balanced view supports our assumption of a constant lung volume, a constant inflow and a decreased expiratory ventilation when using a constant volume ventilator. Our choice was made because we expected the new model to be used mostly for situations where artificial ventilation of the lungs with a pre-set inspiratory volume prevails.

Predictions for the first 3 min of the *F*A/*F*I curves for nitrous oxide are only qualitatively similar to those obtained by Poon, Wiberg and Ward.[4] However, those workers used constant expired ventilation, not constant inspired ventilation. They excluded the effects of dead space ventilation, shunting and storage capacity of lung tissue. Recirculation of anaesthetic was excluded on the basis that their time span of interest was limited to 3 min. By contrast, our results include all these effects.

The increase in the oxygen partial pressure of 4.25 kPa occurring 2.83 min after the introduction of nitrous oxide (Figure 1) is greater than that predicted by Poon and co-workers (3.73 kPa after 3 min)[4] and that experimentally assessed by Shah and colleagues (4.00 kPa).[5] The accompanying increase in the carbon dioxide partial pressure was not predicted by Poon and co-workers, because they assumed constant expired ventilation and therefore maintained normal carbon dioxide elimination—a plausible hypothesis during spontaneous breathing. To the best of our knowledge, an increase in carbon dioxide has been experimentally confirmed in cats,[6] but not in spontaneously breathing humans[5] where normal carbon dioxide regulation would tend to maintain expired ventilation. The increase in carbon dioxide in Figure 1 is probably more than would occur *in vivo* because, in the first few minutes of reduced

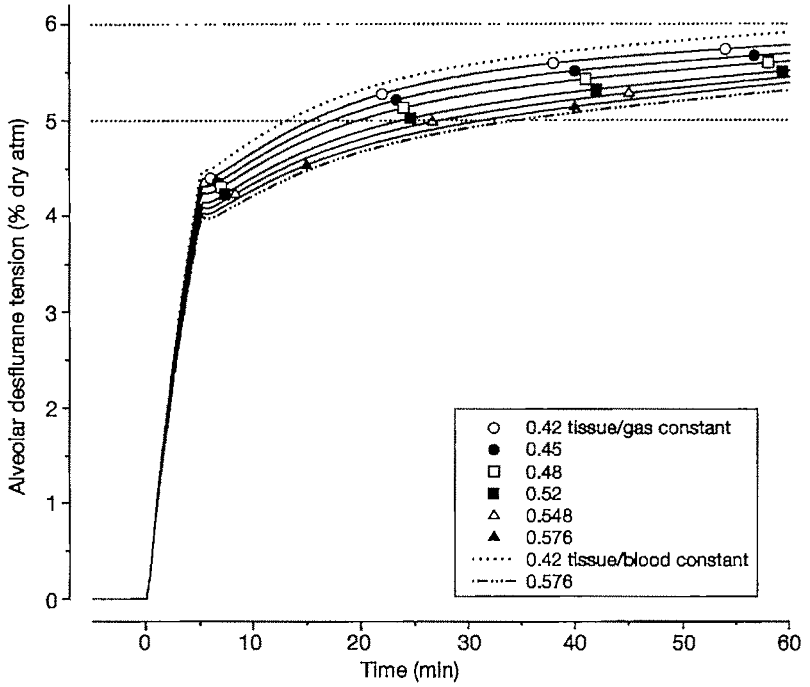

Fig 5 Simulated impact on the alveolar tension of various blood/gas partition coefficients (range 0.42–0.576) for desflurane. The input to the circle system is as in Table 2 (sensitivity analysis with the lower flows for oxygen and nitrous oxide). Time zero is the start of the administration of desflurane. The six continuous lines refer to the assumption of constant tissue/gas partition coefficients. The worst-case, but less likely, scenario of constant tissue/blood partition coefficients is illustrated by the two non-continuous lines obtained with the lowest and highest value for the blood/gas partition coefficient. Obviously, the curves obtained with a blood gas partition coefficient of 0.52 are equal for both scenarios. The horizontal dotted lines are reference lines.

expired ventilation, the alveolar carbon dioxide partial pressure would not increase much above the mixed-venous level: an increase of about 0.8 kPa, not the 1.6 kPa in Figure 1.

Bellows volume

The automated control system behaves well despite counteracting factors, such as the supply of gases being updated only once per 10 s, and the actual 'volume' (*V* in Figure 3) being only part of the total volume to be controlled. The latter is, rather, the volume of the closed circuit plus the unknown volume of the patient's lungs. As the system cannot calculate supply exactly and only makes a good guess, we classify it as a rule-based system. It may eliminate the labour-intensive manual control of CCA.[7] Replacing nitrous oxide with xenon might support research into its use.[8] A major drawback of feedback-controlled closed systems not using a form of forced circulation of gases and charcoal to absorb volatile agents is the slowness of response when changing set points.[9–11]

Sensitivity analysis

The complexity of the model arises from an attempt at physiological fidelity. However, increased complexity may introduce unexpected errors. Predictions deviating from clinical reality can result from errors in the enormous amount of *a priori* information fed to the model, e.g. incorrect blood/gas partition coefficients, or from errors propagating from one gas to another.

The value we chose for the blood/gas partition coefficient of desflurane may be subject to debate. The most cited value is 0.42, but 0.45 has been proposed as the most probable value. The latter is the average of the mean values obtained in two different studies.[12 13] Recently, Lockwood and co-workers[14] reported the values 0.52, 0.548 or 0.576 at a body temperature of 37°C, 36°C or 35°C, respectively. Being obliged to use one value for all simulations, we chose the value 0.52 because Lockwood and co-workers studied more individuals (both patients and volunteers) and we expected that the body temperature of most patients during clinical routine is <37°C. Thus a value of >0.45 seemed justified. The considerable impact of solubility, even at constant tissue/gas partition coefficients, may easily explain discrepancies between predicted and measured concentrations in patients (Figure 5).

Figure 6 illustrates that prediction errors may be generated by a model that does not have the correct inputs for cardiac output and ventilation. Therefore we assume that the curves obtained by using the default values are the ones computed by the model. These curves will differ from those

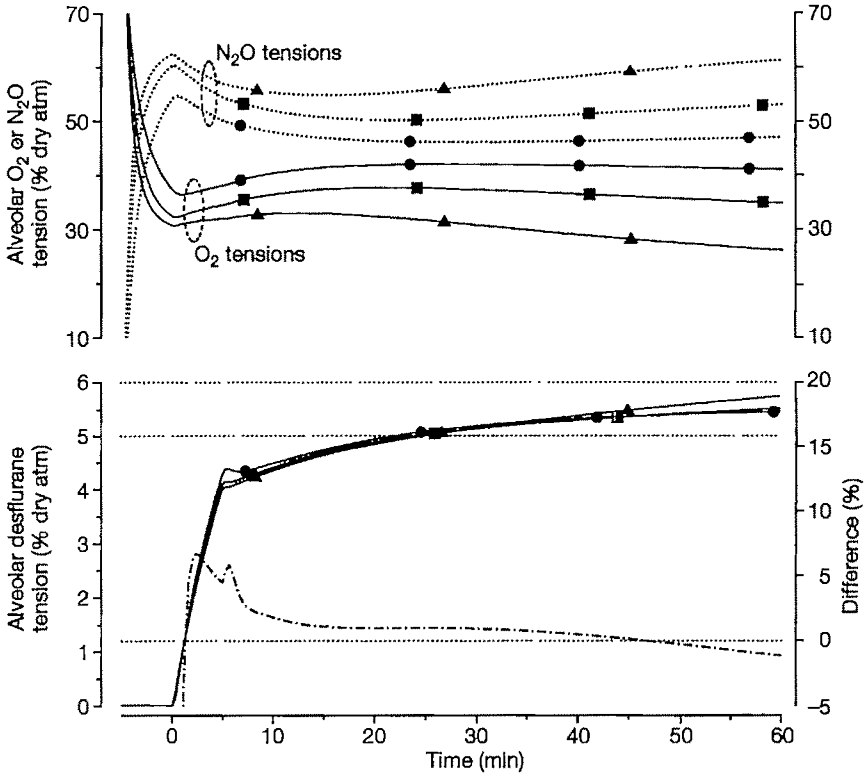

Fig 6 Simulated impact of concomitant changes in oxygen requirement, cardiac output and ventilation on oxygen, nitrous oxide and desflurane kinetics under low-flow conditions. The input to the circle system is as in Table 2 (sensitivity analysis with the higher flows for oxygen and nitrous oxide). Time zero is the start of the administration of desflurane. Squares indicate curves obtained with baseline values for oxygen requirement (201 ml min^{-1} STPD), cardiac output (5.35 litres min^{-1}) and inspired alveolar ventilation (3.60 litres min^{-1} BTPS). Circles indicate a 50% reduction (100.5 mL min^{-1} STPD, 2.67 litres min^{-1}, 1.8 litres min^{-1} BTPS) and triangles a 50% increase (301.5 ml min^{-1} STPD, 8.02 litres min^{-1}, 5.4 litres min^{-1} BTPS) from baseline values. Lower portion: the horizontal dotted lines are reference lines; the line without symbols refers to the percentage differences between baseline circumstances and those with a concomitant reduction in cardiac output and ventilation (squares and circles, respectively).

observed in subjects who have other values, hidden from the observer. In addition, the behaviour of nitrous oxide affects the curves of other gaseous species (Figure 1). Errors made by the model in predicting the uptake of nitrous oxide will propagate, thus disturbing otherwise accurate prediction of concentrations of volatile agents and other gases administered concomitantly. On the other hand, Figure 6 also suggests that certain combinations of physiological variables present in a subject do not necessarily lead to grossly erroneous predictions for desflurane. These findings should not be extrapolated to other conditions of FGF, as the 'openness' of a breathing system affects uptake.[15]

The effects of independent changes in cardiac output were broadly similar to those described by Conway.[16] His model showed that these effects are enhanced by a lower FGF and, in terms of percentage change from control, are greater with a less soluble anaesthetic agent as well as a lower concentration. His results for 2 vol% nitrous oxide in an FGF of 1 litre min^{-1} can thus be compared with ours for desflurane. Halving cardiac output resulted in 13% increase in alveolar concentration for nitrous oxide[16] as compared with 14% for desflurane at the end of a 30 min administration.

Uses of the model

Clinical purposes

During the early stages of anaesthesia, the rate of isoflurane uptake is high and cannot be matched by the limited amount of anaesthetic delivered by a conventional out-of-circle vaporizer under low-flow conditions. The clinically important question, formulated by Mapleson, is then: 'How might the concentration and flow of fresh-gas best be varied during the first few minutes of anaesthesia in order to achieve rapid induction with minimum usage of volatile anaesthetic?'[17] Models are excellent tools to answer such questions, while satisfying the specific requirements of the individual clinician. The clinical use of model-based dosing strategies has yet to be reported.

The initial high flow and subsequent labour-intensive changes of flow and vaporizer settings (Table 2) can be omitted if one uses only one injection of liquid anaesthetic into the expiratory limb of the circle system. This technique[7] achieves total independence of the near-basal FGF (0.5 litres min^{-1}), but the simulated rate of approach to the target is slower (Figure 7). Liquid is assumed to vaporize in the expiratory part of the breathing system over a period of 60 s,

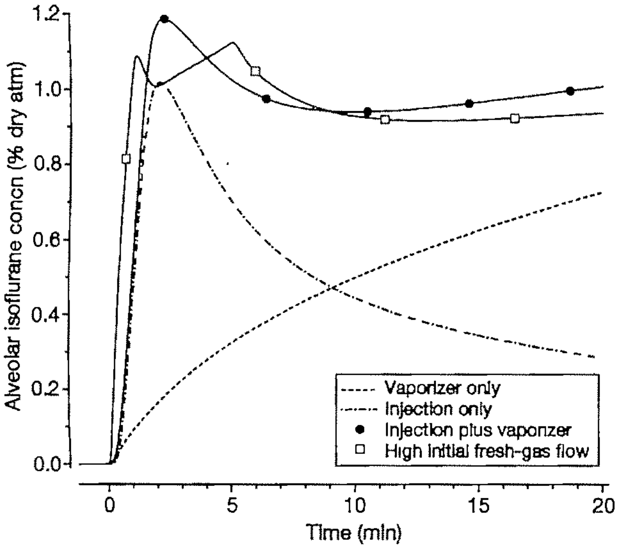

Fig 7 Simulated variation with time of the alveolar isoflurane tension (target window 1 ± 0.1%) resulting from two different dosing strategies (see Table 2) for rapid induction with minimum usage. First strategy: the out-of-circle vaporizer setting is 3.5 vol% (0–5 min) and 2 vol% (5–20 min) in an FGF of 7.5 litres min^{-1} (0–1 min), 1.5 litres min^{-1} (1–5 min) and 1 litres min^{-1} (5–20 min). Second strategy: isoflurane is 'co-administered' through the vaporizer set at 3.5 vol% and a single bolus of 1.25 ml liquid isoflurane injected in the expiratory limb of the circle system (see reference 1, Figure 2) at time zero, using an FGF of 0.5 litres min^{-1}. The two other curves illustrate the effects of using only the vaporizer or only the single injection of liquid isoflurane with 0.5 litres min^{-1} FGF.

whereas the initial high vapour flow is directly introduced into the inspiratory subsystem (see reference [1], Figure 2).

Research and development

Figure 4 (right) suggests how the continuous assessment of oxygen consumption by a monitor based on the replenishment technique might be hampered by noise. A model can indeed aid in determination of the dynamic characteristics of an instrument under less ideal conditions and in testing possible solutions.[18] Given the capabilities and credibility of the model, we can proceed to test and apply the model in the clinical setting.

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Effects of sevoflurane and propofol on pulmonary shunt fraction during one-lung ventilation for thoracic surgery

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Forty patients requiring one-lung ventilation (OLV) for thoracic surgery were randomly assigned to receive propofol (4–6 mg kg^{-1} h^{-1}) or sevoflurane (1 MAC) for maintenance of anaesthesia. Three sets of measurements were taken: (i) after 30 min of two-lung ventilation (TLV), (ii) after 30 min of one-lung ventilation (OLV-1) in the supine position and (iii) during OLV in the lateral position (OLV-2) with the chest open and before surgical manipulation of the lung. There were no differences between groups in patient characteristics or preoperative condition. Increases in shunt fraction during OLV-1 were 17.4% and 17.2% (P=0.94), those during OLV-2 were 18.3% and 16.5% (P=0.59) for the propofol and sevoflurane group, respectively. Cardiac index and other haemodynamic and respiratory variables were similar for the two groups. We conclude that inhibition of hypoxic pulmonary vasoconstriction by sevoflurane may only account for small increases in shunt fraction and that much of the overall shunt fraction during OLV has other causes.

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Hypoxic pulmonary vasoconstriction (HPV) is a mechanism that diverts pulmonary blood flow away from lung regions with low alveolar oxygen tensions to better ventilated areas of the lung, thus reducing venous admixture. Intravenous anaesthetic agents do not seem to affect HPV, whereas in animal experiments, inhalational agents inhibit HPV in a dose-dependent manner, increase intrapulmonary shunt fraction and reduce arterial oxygen tension.[1] *In vitro*, dose-related inhibition of HPV by sevoflurane is comparable to that observed with isoflurane.[2]

Clinical investigations in patients undergoing one-lung ventilation (OLV) have been less conclusive. Two studies failed to detect significant differences in arterial oxygenation between propofol and isoflurane[3] or between isoflurane and sevoflurane anaesthesia.[4] In contrast, Kellow and colleagues[5] found significantly greater shunt fractions during isoflurane anaesthesia than during propofol anaesthesia.

Sevoflurane has useful effects during thoracic surgery. It is a potent bronchodilatator and its low blood–gas partition coefficient allows rapid adjustment of the depth of anaesthesia. Rapid emergence from anaesthesia allows rapid return of spontaneous respiration and avoids the risks of postoperative mechanical ventilation. We compared the effects of sevoflurane and propofol on pulmonary shunt fraction in patients requiring OLV for thoracic surgery.

Patients and methods

After approval by the institutional ethics committee and written informed consent one day before surgery, 40 patients requiring OLV for thoracic surgery were randomized to receive inhalational anaesthesia with sevoflurane (n=20) or intravenous anaesthesia with propofol (n=20).

All patients were premedicated with oral midazolam 0.1 mg kg^{-1} in the ward. In the operating theatre, a radial artery catheter was placed under local anaesthesia. Etomidate 0.2 mg kg^{-1} and fentanyl 0.1–0.2 mg were used to induce anaesthesia. Neuromuscular block was achieved with cisatracurium 0.15 mg kg^{-1}, followed by endobronchial intubation with a left-sided double-lumen tube (Broncho-Cath, Mallinckrodt Medical, Athlone, Ireland) in all patients. The correct position of the tube was initially confirmed by auscultation and the absence of a leak from the lumen connecting to the non-ventilated lung, and by direct observation of the atelectatic, non-ventilated lung after

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thoracotomy. After induction of anaesthesia, a central vein was cannulated and a flow-directed thermodilution catheter (Arrow International, Reading, PA, USA) was placed in the pulmonary artery.

Propofol was infused continuously at an initial rate of 9 mg kg^{-1} h^{-1} which was reduced to 6 mg kg^{-1} h^{-1} after 10 min. Sevoflurane was given to maintain an end-expiratory concentration of 1.8 vol%. Arterial pressure was maintained within 20% of baseline values by administration of crystalloids and fentanyl. Increments of cisatracurium were given to maintain suppression of the second twitch using a train-of-four stimulation.

We used a mixture of oxygen and air to avoid increased venous admixture from absorption atelectasis. The fractional inspired concentration of oxygen was initially set at 0.5 and adjusted to maintain arterial haemoglobin saturation above 91%, measured by pulse oximetry. During two-lung ventilation (TLV) and OLV, tidal volumes of 10 ml kg^{-1} were used with the ventilatory rate adjusted to maintain end-tidal $P\text{CO}_2$ at 35–40 mm Hg. After blood gas analysis, the rate was adjusted to obtain an arterial $P\text{CO}_2$ of 35–45 mm Hg. During OLV, the lumen of the non-ventilated lung remained open to atmosphere; tidal volumes were decreased if peak airway pressure exceeded 35 cm of water. Positive end-expiratory pressure was not applied. The ratio of inspiratory to expiratory time was 1:2.

At the time of measurement, inspiratory and expiratory gas concentrations had been stable for ⩾15 min and were not allowed to change by >10%. All measurements were performed before surgical manipulation of the lung. Cardiac output was measured and mixed-venous and arterial blood gas analysis done (i) after 30 min of TLV with the patient in the supine position; (ii) after 30 min of stable OLV in the supine position (OLV-1); and (iii) after opening of the pleura in the lateral decubitus position and before surgical manipulation of the lung (OLV-2). In patients undergoing thoracoscopy, trocars were left open to atmosphere at the time of measurement (OLV-2). Mixed venous and arterial blood samples were collected in duplicate. Mixed venous blood was drawn over ⩾30 s to avoid inadvertent arterialization. The samples were analysed immediately using a blood gas analyser (ABL 505; Radiometer, Copenhagen, Denmark), which was calibrated daily according to the manufacturer's instructions. The mean of two measurements was recorded. Thermodilution cardiac output was measured by forcible injection of 10 ml of normal saline at room temperature. Measurements were repeated until the difference between three successive readings was <10%. The mean of the readings was recorded as cardiac index. At the same time, haemodynamic variables were recorded, including heart rate, mean arterial and pulmonary artery pressure, pulmonary artery occlusion and central venous pressure (Marquette Electronics, Milwaukee, WI, USA). Inaccuracies in cardiac output measurements could have occurred, because the position of the pulmonary artery catheters was not verified by imaging techniques.

Calculation of shunt fraction

The shunt fraction was computed using a standard formula based on the three-compartment model proposed by Riley and colleagues:[6]

$$Q_s/Q_t=(Cc'_{O_2}-Ca_{O_2})/(Cc'_{O_2}-Cv_{O_2})$$

where Q_s=shunt flow, Q_t=cardiac output and Cc'_{O_2}, Ca_{O_2} and Cv_{O_2} represent the oxygen content of pulmonary end-capillary, arterial and mixed venous blood, respectively. Arterial and mixed venous oxygen content were calculated according to the formula

$$Co_2=Po_2\times 0.0031+(\text{Hb}\times 1.34So_2/100)$$

where Po_2 and So_2 represent the partial pressure (mm Hg) and oxyhaemoglobin saturation in the arterial (Ca_{O_2}) or mixed venous (Cv_{O_2}) blood. Arterial and mixed venous Po_2 and So_2 can be directly measured. In the case of Cc'_{O_2} the relevant partial pressure and saturation have to be derived from the alveolar oxygen tension (PA_{O_2}):

$$PA_{O_2}=FI_{O_2}\times(PB-PH_2O)-(Pa_{CO_2}/R)$$

where FI_{O_2} is the fractional inspired oxygen concentration, PB is barometric pressure, PH_2O is the saturated vapour pressure of water (47 mm Hg) at body temperature, Pa_{CO_2} is arterial carbon dioxide partial pressure and R is the respiratory quotient (assumed to be 0.8). Therefore, $Cc'_{O_2}=PA_{O_2}\times 0.0031+(1.34\text{Hb})$. The actual barometric pressure was recorded before each measurement. PA_{CO_2} tension was assumed to equal Pa_{CO_2} and an assumption was made that the haemoglobin would be 100% saturated.

The sample size was estimated using the data of a previous investigation.[16] A difference of 8.5% in the mean increase of shunt fraction between the groups and a standard deviation of 9.3% were used for the calculation. Forty patients would be required to give 80% probability (power) of demonstrating this difference at the 5% significance level.

Statistical analysis

One-way analysis of variance (ANOVA) was used to test the difference between the means of normally distributed data. Simple linear regression was used to analyse the relationship between cardiac index (predictor variable) and shunt fraction (dependent variable). We applied best subsets linear regression analysis to assess the association between five predictor variables and the dependent variable (shunt fraction). This technique allows a systematic search of the different combinations of predictor veriables, selecting those subsets that best contribute to the variation of the dependent variable. We tested five variables: cardiac index, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), $P\bar{v}_{O_2}$) and Pa_{CO_2}. We decided not to test derived variables such as pulmonary and systemic arterial resistance, since their calculation uses haemodynamic variables included in the analysis (cardiac output, MAP and MPAP). We finally did a *post hoc* power analysis to assess the sensitivity of the study to detect a true difference between the groups.

Results

Forty patients were enrolled in the study. Two patients, one from each group, were excluded from analysis because hypotensive episodes during induction of anaesthesia required vasoactive drugs to be given. Patient details, preoperative lung function tests and blood gas values were similar in the two treatment groups (Table 1). Twenty patients had thoracotomy, nine in the propofol and 11 in the sevoflurane group; nine right-sided and 11 left-sided thoracotomies were performed. Eighteen patients, 10 in the propofol group and eight in the sevoflurane group, had video-assisted thoracoscopic procedures, of which 11 involved the left and seven the right hemithorax (Table 2). Seven patients in the propofol group and eight in the sevoflurane group required FI_{O_2} concentrations of >0.5 to keep arterial oxygen saturation above 91%.

Compared with the baseline measurements (TLV), average shunt fractions during OLV-1 increased by 17.4% and 17.2% (P=0.94), and those during OLV-2 by 18.3% and 16.5% (P=0.59) for the propofol and sevoflurane group, respectively (Figure 1). There were no significant differences in haemodynamic and respiratory variables between the groups (Table 3). In particular, those variables known to influence HPV directly, such as cardiac index, mixed-venous oxygen tension and arterial carbon dioxide partial pressure, did not differ significantly between the treatment groups. Thus, possible effects on calculated shunt fraction resulting from these confounding variables can be assumed to have been of similar magnitude for both groups. For the range of values of cardiac output and shunt fraction observed in our study population, simple linear regression analysis showed a positive trend, but no significant correlation between cardiac index and shunt fraction. This is described by the regression equation y=19.775+2.95x (P=0.06; correlation coefficient r=0.230). Best subsets regression analysis showed that only two variables contributed significantly to the variation in shunt fraction, namely cardiac index (P=0.02) and Pa_{CO_2} (P=0.04). $P\bar{v}_{O_2}$ (P=0.09) and the other haemodynamic variables tested did not explain changes in shunt fraction (MAP, P=0.43; MPAP, P=0.45).

The results of the *post hoc* power analysis using the data from our study showed that there was an 80% probability (power) of detecting an 8.5% difference in the mean increase of shunt fractions (TLV to OLV-2) between the groups. The probability of demonstrating a 10.5% difference was 90%. Both calculations were performed using a standard deviation of 9.1% and a significance level of 5%.

Table 1 Patient details, lung function tests and preoperative laboratory investigations; values are mean±SD, except for age (mean and range). BMI=body mass index, FEV_1=forced expiratory vital capacity, FVC=forced vital capacity

	Propofol (n=19)	Sevoflurane (n=19)
Age (yr)	62 (46–78)	58 (34–78)
Females	6	7
BMI (kg m^{-2})	24.3 (3.4)	23.1 (4.3)
Haemoglobin (g dl^{-1})	13.2 (1.6)	11.9 (2.3)
Pa_{O_2} (mm Hg)	66.9 (9.8)	76.1 (8.2)
Pa_{CO_2} (mm Hg)	40.0 (3.5)	39.2 (4.8)
Oxygen saturation (%)	92.4 (3.2)	93.8 (3.0)
FEV_1 (litres s^{-1})	2.2 (0.9)	2.7 (0.5)
% of predicted FEV_1	85.3 (30.1)	84.5 (13.3)
FVC (litres)	2.8 (1.0)	3.4 (0.7)
% of predicted FVC	87.2 (27.3)	87.9 (10.6)

Table 2 Type and side of surgical procedures; VA refers to video-assisted thoracoscopic operations

Operation	Propofol (n=19)	Sevoflurane (n=19)
Thoracotomies		
Right pneumonectomy	1	2
Right lobectomy	2	2
Left lobectomy	5	6
Right pleurectomy	1	1
Total	9	11
VA procedures		
VA–right lobectomy	2	1
VA–left lobectomy	3	2
VA–atypical resection, right	1	3
VA–atypical resection, left	4	2
Total	10	8

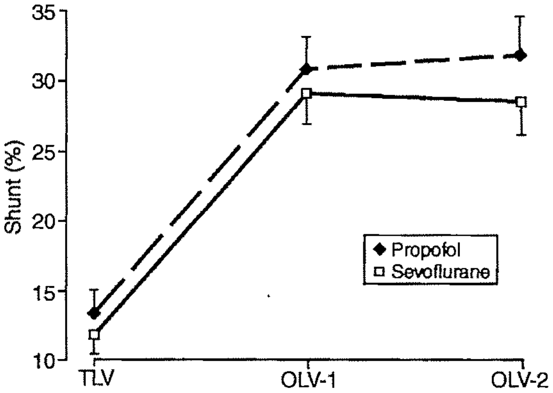

Fig 1 Measurements of shunt at the three measurement times. TLV=two-lung ventilation; OLV-1, one-lung ventilation, supine; OLV-2, one-lung ventilation, lateral. Error bars represent SEM.

Discussion

Compared with propofol, the administration of sevoflurane resulted in similar increases in shunt fraction during OLV. Small increases in shunt fraction by direct inhibition of the

Table 3 Haemodynamic measurements, $P\bar{v}_{O_2}$, Pa_{O_2} and shunt fraction; values are mean (SD). TLV=two-lung ventilation; OLV-1=one-lung ventilation, supine position; OLV-2=one-lung ventilation, lateral position; HR=heart rate; MAP=mean arterial pressure (mm Hg); CVP=central venous pressure (cm H_2O); PCOP=pulmonary capillary occlusion pressure (mm Hg), MPAP=mean pulmonary artery pressure (mm Hg); SVRI and PVRI=systemic and pulmonary vascular resistance index (dyn s cm^{-5} m^2); CI=cardiac index (litres min^{-1} m^2); Pa_{CO_2}=arterial carbon dioxide tension (mm Hg); $P\bar{v}_{O_2}$ and Pa_{O_2} =mixed venous and arterial oxygen tension (mm Hg)

	HR	MAP	CVP	PCWP	MPAP	SVRI	PVRI	CI	% Shunt	$P\bar{v}_{O_2}$	Pa_{O_2}	Pa_{CO_2}
TLV												
Propofol	71 (46–109)	87 (21)	11 (3)	12 (3)	23 (7)	2177 (699)	316 (206)	2.5 (0.5)	13.4 (6.9)	41 (5)	168 (59)	42 (8)
Sevoflurane	67 (48–80)	69 (14)	12 (4)	15 (3)	20 (5)	1815 (870)	215 (101)	2.4 (0.6)	11.8 (5.4)	43 (7)	184 (66)	41 (6)
OLV-1												
Propofol	70 (47–104)	80 (16)	11 (4)	13 (2)	23 (7)	1985 (592)	411 (217)	2.7 (0.8)	30.8 (9.7)	39 (4)	91 (23)	46 (7)
Sevoflurane	71 (52–108)	70 (11)	12 (3)	14 (3)	22 (5)	1703 (383)	296 (122)	2.6 (0.6)	29.0 (8.9)	40 (6)	103 (52)	43 (6)
OLV-2												
Propofol	70 (50–101)	104 (17)	13 (5)	15 (4)	25 (7)	2811 (807)	322 (181)	2.7 (0.6)	31.7 (11.5)	40 (6)	104 (66)	44 (7)
Sevoflurane	77 (55–107)	93 (20)	14 (4)	17 (4)	26 (7)	2323 (935)	348 (152)	2.8 (0.8)	28.3 (9.2)	41 (7)	100 (33)	42 (6)

HPV response by sevoflurane could have been opposed by improved ventilation–perfusion (*V*/*Q*) matching during OLV and, consequently, reduced venous admixture.

Inhibition of the HPV response by inhalational anaesthetics is well established in animals. Depression of HPV has a typical sigmoid dose–response curve with an effective dose (ED_{50}) slightly less than twice the minimal alveolar concentration (MAC) and an ED_{90} of 3 MAC. There is no major difference between the volatile anaesthetics.[17] During inhalational anaesthesia at 1 MAC (1.8 vol%) of sevoflurane, the HPV response would be reduced by approximately 25%.[2]

Cardiac output, mixed venous Po_2 and lung perfusion

There are several reasons for the failure to reproduce these findings in the clinical context. The conflicting results obtained from human studies comparing intravenous and volatile anaesthetic agents in patients undergoing OLV have been widely attributed to haemodynamic changes, particularly the reduction of cardiac output, which may be more pronounced especially with the older volatile agents. The efficacy of HPV is inversely related to the cardiac output,[8] but interactions between several physiological variables can obscure the effects of cardiac output on HPV and shunt fraction in the clinical setting. A reduction in cardiac output will decrease $P\bar{v}_{O_2}$ and increase pulmonary vasoconstriction. Volatile agents inhibit HPV by direct action, but at the same time augmentation of the HPV response occurs from decreasing cardiac output. Consequently, pulmonary shunt fraction and, by inference, HPV will appear to be unaffected.[9]

The HPV response is a function of both mixed venous and alveolar oxygen tension (PA_{O_2}).[10] During OLV, the PA_{O_2} of the non-ventilated, atelectatic lung can be assumed to equilibrate with the $P\bar{v}_{O_2}$. In animal experiments, low and normal $P\bar{v}_{O_2}$ values between 25 and 46 mm Hg (3.2–6.1 kPa) cause maximal diversion of the blood flow (40–50%) away from the collapsed lung.[11] Hambraeus-Jonzon and colleagues,[12] however, showed that during unilateral hypoxic ventilation (FI_{O_2}=0.05) and hyperoxic ventilation of the other lung (FI_{O_2} =1.0) in humans, the moderate decrease in $P\bar{v}_{O_2}$ made only a minor contribution to blood flow diversion compared with the reduction in alveolar Po_2.

Variations in cardiac output not only influence $P\bar{v}_{O_2}$ but also affect pulmonary perfusion. Domino and colleagues[13] demonstrated that marked increases in cardiac output will increase pulmonary perfusion and worsen ventilation—perfusion mismatch; a 50% increase in pulmonary blood flow increased *V*/*Q* heterogeneity by 25%. On the other hand, low cardiac output can cause inhomogeneous distribution of blood flow in the ventilated lung with similar consequences for the ventilation–perfusion ratio. The effects of changes in cardiac output and subsequent alterations in $P\bar{v}_{O_2}$ and lung perfusionare difficult to separate during OLV, but $P\bar{v}_{O_2}$ values are usually within the range at which maximal stimulation of the HPV response occurs. Only dramatic changes in cardiac output and pulmonary perfusion will attenuate this response. In the present study, cardiac index and $P\bar{v}_{O_2}$ values were similar for both treatment groups and are therefore unlikely to cause differences in shunt fractions between the groups.

V/Q scatter and bronchodilation

The method we used to derive shunt fraction does not allow distinction between venous admixture resulting from perfusion of non-ventilated lung regions ('true shunt') with ventilation–perfusion ratios of zero (*V*/*Q*=0) and lung regions that are perfused, but poorly ventilated and therefore have low, but not zero, *V*/*Q* ratios. Ventilation–perfusion mismatch is often present in patients undergoing lung resection surgery. Sevoflurane may have caused more uniform distribution of ventilation to the dependent lung during OLV, thereby decreasing shunt fraction. This could have opposed or even overcome the increase in venous admixture from inhibition of the HPV response.

The increase in shunt fraction by direct inhibition of HPV by inhalational anaesthetics administered in concentrations of 1 MAC can be expected to be rather small.[1] Despite maximal stimulation of the HPV response, there will be an obligatory shunt fraction of 25% during OLV.[12 14] Attenuation of the maximal HPV response by 25% would increase shunt fraction from 25% to 30% in the presence of 1 MAC sevoflurane, provided other confounding variables remain unchanged. Thus, direct inhibition of HPV could cause a 5% increase in shunt fraction.

Shunt fraction in clinical investigations

Propofol in doses of 6–12 mg kg^{-1} h^{-1} had no significant effect on Pa_{O_2} or shunt fraction.[15] Reports comparing propofol with volatile agents overestimated the effects of direct inhibition of HPV by volatile agents, since shunt fractions increased more than expected from animal data. Shunt fractions during OLV were greater in patients who had received enflurane[16] (1 MAC) and isoflurane[5] (1 MAC). In both studies, shunt fractions were derived from oxygenation indices in a similiar manner to the present study.

Carlsson and colleagues[17 18] applied multiple inert gas elimination techniques to investigate the influence of isoflurane and enflurane on HPV in human lungs. This complex method allows accurate measurement of the 'true' shunt fraction. The authors found a 2–3% increase in shunt fraction after administration of 1.5 vol% isoflurane, which corresponded to an attenuation of the HPV response by 20%. They found that effects on hypoxia-induced pulmonary vasoconstriction were almost immeasurable when isoflurane was administered in clinically used concentrations. Similarly, up to 2 MAC of enflurane caused no significant change in shunt or arterial oxygenation.

Abe and colleagues[19] investigated the effects of propofol, sevoflurane and isoflurane in patients undergoing oesophageal surgery and concluded that the administration of propofol was associated with significantly improved oxygenation and lower shunt fractions. However, the experimental sequence was such that the volatile agents always preceded propofol. The reduction in shunt fraction may be because propofol was always given at a later stage of surgery and after a longer period of OLV.

The timing of the measurements and their relation to the stage of the surgical procedure is important since surgical trauma can temporarily inhibit HPV.[20] We made measurements before surgical manipulation of the non-ventilated lung. Beside the direct effects of surgical trauma to lung tissues, the efficacy of HPV response may vary with the duration of OLV. Rees and colleagues found a maximal increase in shunt fraction after 30 min of OLV during enflurane anaesthesia.[21] In patients who required prolonged OLV for oesophageal surgery, oxygenation improved significantly over time. Minimal Pa_{O_2} values occurred after 30 min and reached a maximum after 90 min of OLV.[22 23]

For our patients, simple linear regression showed a positive trend, but no significant correlation, between cardiac index and shunt fraction during OLV, consistent with the postulated inverse relationship between cardiac output and HPV response.[8] Other investigators,[24] however, reported improved arterial oxygenation with increasing cardiac output. Best subsets regression analysis showed that only cardiac index and Pa_{CO_2} contributed significantly to the variations in shunt fraction. Mixed venous oxygen tension, which is also thought to affect the HPV response, did not explain changes in shunt fraction. This supports the view that the attenuation of the HPV response occurs at much lower $P\bar{v}_{O_2}$ values than those usually achieved during OLV.

In summary, sevoflurane administered in clinical concentrations of 1 MAC resulted in similar changes in shunt fraction as did propofol. Cardiac index, mixed $P\bar{v}_{O_2}$ and Pa_{CO_2} did not differ between the groups. Much of the overall shunt fraction during OLV may result from sources other than the attenuation of the HPV response. Haemodynamic stability and appropriate ventilatory manoeuvres are probably far more important for achieving optimal arterial oxygenation during OLV than is the choice of the anaesthetic agent.

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Recovery and neurological examination after remifentanil–desflurane or fentanyl–desflurane anaesthesia for carotid artery surgery

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We studied 44 patients undergoing carotid endarterectomy (CEA) to compare recovery after general anaesthesia with desflurane supplemented with either remifentanil or fentanyl. Remifentanil was infused at 0.1 $\mu g\ kg^{-1}\ min^{-1}$ and desflurane was adjusted at 2 vol% end-tidal. Fentanyl was given as a bolus dose of 2 $\mu g\ kg^{-1}$ before induction and repeated at skin incision; desflurane was adjusted as needed. Times for early recovery and response to simple neurological tests (digit symbol substitution test (DSST) and Trieger dot test (TDT)) were measured 30, 60 and 90 min after operation. Emergence from remifentanil–desflurane anaesthesia was significantly quicker than that from fentanyl–desflurane anaesthesia: mean times to extubation were 4.1 (SD 1.7) and 8.2 (4.9) min, respectively; mean times for patients to state their name correctly were 6.0 (2.8) and 13.8 (9.0) min, respectively. Patients in the remifentanil–desflurane group successfully performed neurological tests significantly earlier than those in the fentanyl-desflurane group; for example, patients in the former group completed the arm holding test at 7.9 (3.0) min, while those in the latter group did this at 20.6 (19.7) min ($P \leq 0.01$). Intermediate recovery was less impaired at 30 min (DSST, TDT) and at 60 min (DSST). More rapid awakening and an earlier opportunity for neurological examination suggest that remifentanil–desflurane is a suitable alternative to a standard fentanyl-based general anaesthetic technique in patients undergoing CEA.

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Carotid artery surgery carries the risk of substantial complications; in some cases (such as dissection, thrombosis or haemorrhage), the damage can be reduced if complications are diagnosed early and treated promptly.[1–3] Therefore, rapid recovery and early neurological assessment are useful goals in the anaesthetic management of patients undergoing carotid endarterectomy (CEA). The combination of short-acting anaesthetics such as remifentanil and desflurane may be superior to a standard fentanyl general anaesthetic technique. We compared early and neurological testing of patients undergoing elective CEA who were randomly assigned to receive general anaesthesia with remifentanil–desflurane or fentanyl-desflurane.

Patients and methods

Preinduction

With institutional review board approval and written informed consent, we enrolled 44 adult male and female patients in a prospective randomized two-group study. All patients were classified as ASA physical status II or III and scheduled for elective CEA because of a narrowing of the carotid artery lumen of ≥80% in asymptomatic or ≥70% in symptomatic patients. Exclusion criteria were a history of any disabling central nervous disease, hypersensitivity to opioids or substance abuse, or a treatment with opioids or

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any psychoactive medication. After enrollment patients were randomized by drawing lots from a closed box.

Induction and maintenance

On the morning of surgery, all patients were given 5 mg of diazepam orally 90 min before induction. In the operating room, two intravenous catheters were inserted and the radial artery was cannulated. Standard monitors were applied. Before induction, all patients were given 5 ml kg^{-1} of a 3% gelatin infusion intravenously.

In the fentanyl–desflurane group, induction started with a dose of fentanyl 2 $\mu g\ kg^{-1}$. Five minutes later etomidate was given for hypnosis, initially starting at 0.15 mg kg^{-1} and then at 2 mg every 10 s until the patient was unresponsive to verbal command. The desflurane vaporizer was then set to 3 vol% and ventilation with desflurane in oxygen was given as required. Patients were then given 0.1 mg kg^{-1} of cisatracurium, the trachea was intubated 3 min later and the lungs were ventilated to achieve normocapnia, using desflurane and 66% nitrous oxide in oxygen. Five minutes before skin incision, another 2 $\mu g\ kg^{-1}$ bolus dose of fentanyl was injected and desflurane was added as needed for maintenance, starting at an end-tidal concentration of 4 vol% (=2/3 MAC).

In the remifentanil–desflurane group, all patients were given atropine 5 $\mu g\ kg^{-1}$ followed by remifentanil 1 $\mu g\ kg^{-1}$, injected over 30 s, and an infusion of remifentanil was started simultaneously at 0.1 $\mu g\ kg^{-1}\ min^{-1}$. Five minutes later, etomidate was given, followed by desflurane and cisatracurium as described above. Five minutes after intubation remifentanil was reduced to 0.05 $\mu g\ kg^{-1}\ min^{-1}$ and then readjusted to 0.1 $\mu g\ kg^{-1}\ min^{-1}$ 3 min before skin incision. Maintenance of anaesthesia consisted of remifentanil infused at 0.1 $\mu g\ kg^{-1}\ min^{-1}$, with desflurane added to obtain an end-tidal concentration of 2 vol% (=1/3 MAC).

In both groups, according to our department's policy, nitrous oxide was discontinued 5 min before the carotid artery was cross-clamped; the lungs were then ventilated with desflurane in oxygen until the end of the operation.

Monitoring and haemodynamic control

Continuous monitoring included heart rate (HR), systemic arterial pressure, respiratory rate, oxygen saturation and end-tidal concentrations of carbon dioxide and desflurane. Arterial blood gases were analysed intermittently and the Pa_{CO_2} was maintained between 4.8–5.9 kPa (36–44 mm Hg). The oxygen saturation was measured by pulse oximetry and maintained above 95%. Transcranial Doppler ultrasound was continuously applied, by a neurologist (M.M.), to the ipsilateral middle cerebral artery to measure mean blood velocity during surgery and cross-clamping (for the exact technique see ref. 4).

Baseline systolic arterial pressure (SAP) was defined as the lower of the two measurements obtained the day before surgery and immediately before induction of anaesthesia. The definition of adverse haemodynamic responses was adapted from Garrioch and Fitch:[1] responses of ≥1 min of duration were classified as 'hypertension' (SAP>40 mm Hg from baseline or >200 mm Hg), 'hypotension' (SAP<40 mm Hg from baseline or <100 mm Hg), 'tachycardia' (HR>100 beats min^{-1}) and 'bradycardia' (HR<45 beats min^{-1}). Inadequate anaesthesia was defined as hypertension, tachycardia or patient movement, eye opening, swallowing, grimacing, lacrimation or sweating.

In the fentanyl–desflurane group, if anaesthesia was inadequate the end-tidal desflurane concentration was increased in steps of 0.5 vol% as necessary. If this was judged insufficient, then an additional bolus dose of 0.5 $\mu g\ kg^{-1}$ fentanyl could be injected. Hypotension was initially treated with i.v. fluid replacement; desflurane was then reduced in steps of 0.5 vol%, and finally, an i.v. vasopressor (cafedrine/theodrenaline) was given at a dose chosen by the investigator. In the remifentanil–desflurane group, if anaesthesia was inadequate the infusion rate was increased by 0.05 $\mu g\ kg^{-1}\ min^{-1}$ or a bolus dose of 1 $\mu g\ kg^{-1}$ was injected; both interventions were repeated as necessary. If this was insufficient, desflurane was increased by 0.5 vol% end-tidal. Hypotension was initially treated with i.v. fluids; the remifentanil infusion rate was then reduced to a permitted minimum of 0.05 $\mu g\ kg^{-1}\ min^{-1}$; finally, an i.v. vasopressor was used as described above. In both groups bradycardia was treated with 0.25 mg of atropine.

Recovery period

Fifteen minutes before the expected end of surgery, complete neuromuscular recovery was ensured by neuromuscular monitoring; all patients received a 100 ml infusion of 0.9% NaCl containing metamizol 25 mg kg^{-1} for postoperative pain relief. The end of surgery was defined as the final surgical suture, when anaesthetic delivery was stopped. During recovery, a post-anaesthetic recovery score (PARS), as defined by Aldrete and Kroulik,[5] was recorded continuously. Oxygenation was maintained by intermittent positive pressure ventilation using a fresh gas flow of 10 litres min^{-1} of 100% oxygen until spontaneous respiration returned. Emergence from anaesthesia was assessed by measuring the times to return of spontaneous ventilation, extubation, response to verbal command (opening eyes, stating name and date of birth) and when the Aldrete score became 9 or above.

All patients were then moved to the post-anaesthesia care unit (PACU), where observation was continued by an investigator and a PACU nurse, neither of whom was aware of the anaesthetic regimen. If further pain relief was requested, patients could be given bolus doses of 3 mg piritramide at the discretion of the attending nurse. Each patient was continuously observed for neurological deficits, and the times (expressed as minutes from end of surgery) taken for the patient to be able to perform the arm and the leg holding tests were recorded. The depth of sedation was assessed for the first 60 min after the end of surgery using a five-point scale for observer assessment of alertness/sedation: 1=asleep, unarousable; 2=asleep, difficult to rouse; 3=asleep, easy to rouse; 4=awake and calm; 5=awake but anxious.

Intermediate recovery was assessed by the Trieger dot test (TDT), in which individuals are asked to connect a series of 50 dots of a geometrical figure,[6] and by the digit symbol substitution test (DSST), in which individuals are asked to match numbers with predefined symbols during a 120 s period (adapted from refs [7] and [8]). All patients had completed a first series of these tests on the day before surgery, with the results serving as baseline values. Thirty, 60 and 90 min after the end of surgery, both tests were repeated; the results are expressed as a percentage of baseline.

Table 1 Patient, surgical, anaesthetic and neurological characteristics; values are mean (SD) or number of patients (% of total group). CXC=carotid artery cross-clamping. †End-tidal desflurane concentration at the end of surgery without tapering. *Significant difference between the two treatment groups ($P<0.05$)

	Remifentanil–desflurane	Fentanyl–desflurane
Number of patients	23	21
Gender (male/female)	16/7	12/9
Age (yr)	64.0 (44–76)	62.4 (43–77)
Height (cm)	168.2 (7.1)	167.6 (7.9)
Weight (kg)	73.5 (9.8)	77.6 (10.5)
ASA physical status, *n* (%)		
ASA II	4 (17%)	5 (24%)
ASA III	19 (83%)	16 (76%)
Duration of surgery (min)	100.9 (23.0)	110.4 (18.1)
Side of operation (left/right)	16/7	5/16*
Duration of anaesthesia (min)	138.5 (25.6)	148.8 (19.6)
Fentanyl (mg)	–	0.35 (0.1)
Etomidate (mg)	20.7 (5.5)	25.5 (7.3)*
Desflurane (vol%)†	1.9 (0.2)	3.5 (1.4)*
Duration of CXC (min)		
Without shunt	44.4 (13.1) (*n*=19)	49.8 (18.8) (*n*=18)
With shunt	9.8 (5.9) (*n*=4)	10.3 (5.7) (*n*=3)

End-points and statistical analysis

The primary end-point of this study was defined as the time taken to respond to verbal command (state the correct name). Applying an *a priori* power analysis, at least 17 patients had to be enrolled in each treatment group to provide 80% power to detect a difference of 3 min at $\alpha=0.05$. Statistical analysis was performed by means of the Mann–Whitney *U*-test for numerical data and Fisher's exact test for nominal data. All tests were two-tailed with statistical significance defined as $P<0.05$; data are presented as mean and standard deviation (SD) in the tables or standard error (SEM) in the figures. Statistical analysis was planned and performed in collaboration with a statistician of the Institute of Medical Biometrics, Epidemiology and Informatics, University of Saarland, using SPSS computer software (version 7.5.2G; SPSS Inc.).

Results

Forty-four patients were enrolled in this study (23 in the remifentanil group and 21 in the fentanyl group); the groups were similar with respect to age, weight, height, ASA physical status and duration of surgery (Table 1). With remifentanil, less etomidate was necessary to achieve a loss of consciousness during induction of anaesthesia. At the end of surgery, the mean end-tidal desflurane concentration was significantly lower (1.9 (SD 0.2) vol%) than with fentanyl (3.5 (1.4) vol%). Carotid artery cross-clamping times were similar in both groups but, by chance, significantly more patients with remifentanil–desflurane had surgery on the left (dominant hemisphere) side.

Overall, haemodynamic responses (i.e. the courses of HR and mean arterial pressure) were similar for both treatment groups: mean arterial pressure did not differ throughout surgery and was significantly less with remifentanil than with fentanyl only immediately before and 1 min after intubation (Table 2). Intervention with a vasopressor (cafedrine/theodrenaline) was used in 70% of all patients (78% with remifentanil, 62% with fentanyl ($P=0.33$)) and there was no difference in the amount of drug given per treated patient (0.92 (0.61) or 0.92 (0.43) ml).

Table 2 Mean (SD) cardiovascular variables before and after induction of anaesthesia and during carotid artery sugery; $^*P<0.05$ and $^{**}P<0.01$ between groups. CXC=carotid artery cross-clamping

	Mean arterial pressure (mm Hg)		Heart rate (bpm)	
	Remifentanil–desflurane	Fentanyl–desflurane	Remifentanil–desflurane	Fentanyl–desflurane
Baseline	111.7 (17.5)	116.4 (13.6)	74.7 (11.1)	78.0 (14.3)
Before intubation	82.7 (16.0)	92.7 (16.0)*	62.1 (13.3)	66.5 (11.6)
1 min after intubation	110.9 (23.1)	131.8 (24.9)**	76.3 (15.0)	86.2 (20.5)
5 min after intubation	95.7 (22.7)	93.4 (20.5)	67.3 (15.2)	69.0 (15.8)
Before CXC	93.7 (16.0)	92.1 (11.9)	64.3 (8.3)	73.1 (14.1)*
End of surgery	86.1 (17.4)	90.4 (12.7)	63.1 (8.7)	65.5 (11.3)

Table 3 Recovery times (min) after discontinuation of anaesthetics. PARS=Post-anaesthetic recovery score. Values are mean (SD); n=number of patients

	Remifentanil–desflurane (n=22)	**Fentanyl–desflurane (n=20)**	***P***
Spontaneous ventilation	3.9 (1.6)	6.4 (5.0)	0.09
Opening eyes	3.8 (1.6)	8.0 (5.3)	<0.01
Extubation	4.1 (1.7)	8.2 (4.9)	<0.01
Stating name	6.0 (2.8)	13.8 (9.0)	<0.001
Stating date of birth	6.2 (2.8)	14.9 (10.8)	<0.001
PARS ≥9	6.4 (2.9)	16.4 (17.7)	<0.01
Arm holding test	7.9 (3.0)	20.6 (19.7)	<0.001
Leg holding test	12.2 (17.6)	33.9 (27.6)	<0.001

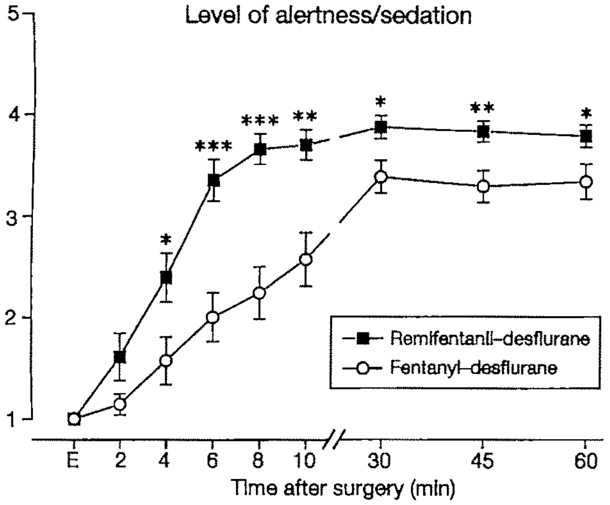

Fig 1 Mean (SEM) scores of an observer-assessed alertness/sedation scale (1=asleep, unarousable; 2=asleep, difficult to rouse; 3=asleep, easy to rouse; 4=awake and calm; 5=awake but anxious). E=End of surgery. Differences between the treatment groups were statistically significant: ***$P<0.001$, **$P<0.01$ and *$P<0.05$.

Recovery period

After awakening, a major stroke was found in one patient in each treatment group. Consequently, early recovery times were recorded for 22 patients in the remifentanil group and for 20 patients in the fentanyl group. Apart from the onset of spontaneous ventilation, recovery times were significantly shorter after remifentanil–desflurane: tracheal extubation was possible sooner and patients could open their eyes sooner and state their name and date of birth correctly sooner. Neurological tests could be carried out significantly earlier (Table 3).

The sedation score showed that patients after remifentanil–desflurane anaesthesia were significantly more alert than those after fentanyl–desflurane anaesthesia, and a significant difference was noted even 60 min after the end of surgery (Figure 1).

Psychomotor and cognitive performance was assessed by DSST and TDT scores in 20 patients in each group. Two patients in the remifentanil group could not be investigated: one patient underwent surgical treatment for superficial wound bleeding, and another refused to participate in that part of the study. Both tests showed an initial decrease from baseline values and than progessively improved during the period of emergence. Following remifentanil–desflurane anaesthesia, DSST and TDT were impaired significantly less at 30 min (DSST, TDT) and 60 min (DSST) after anaesthesia (Figures 2 and 3).

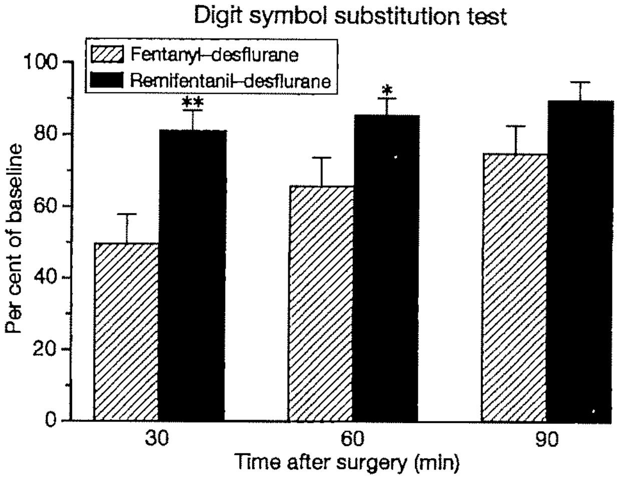

Fig 2 Mean (SEM) results of the digit symbol substitution test 30, 60 and 90 min after the end of surgery, expressed as percentage of baseline. Differences between the treatment groups were statistically significant: **$P<0.01$, *$P<0.05$.

Discussion

We found that patients undergoing carotid artery surgery after remifentanil–desflurane anaesthesia recovered more quickly than those given a 'traditional' general anaesthetic technique with intermittent bolus doses of supplemental fentanyl. This acceleration of recovery is not limited to the initial period of awakening from anaesthesia; it also allows earlier neurological examination and is still shown in the first hour after surgery with a more rapid return of psychomotor and cognitive functions.

These results are of current interest since CEA is increasingly being performed in patients with carotid stenosis, and randomized clinical studies have shown that strokes can be reduced.[9] However, CEA may cause postoperative neurological deficits, which should be diagnosed and treated promptly. In some techniques, the use of opioids is reduced whenever possible to allow rapid postoperative awakening and early neurological assessment.[2] Other techniques use an opioid-based anaesthetic because of the prevalence of co-existing coronary artery disease in these patients.[1]

Remifentanil is rapidly broken down by non-specific esterases to nearly inactive metabolites, so recovery from intraoperative opioid analgesia can be rapid.[10] After remifentanil, about 2 min elapsed from the onset of spontaneous ventilation to the moment that patients could state their name and date of birth correctly, and 2 min later

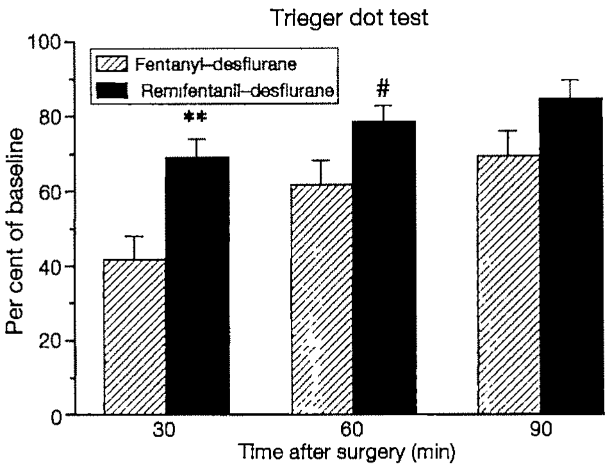

Fig 3 Mean (SEM) results of the Trieger dot test 30, 60 and 90 min after the end of surgery, expressed as percentage of baseline. Differences between the treatment groups: **P<0.01, #P=0.05.

patients could be examined neurologically by the arm holding test. The sedation score, DSST and TDT results, showed that intermediate recovery was also shorter.

The properties of remifentanil allow high-dose opioid use throughout the operation, and reduce the amount of desflurane needed, which is a reason for the difference in recovery seen when remifentanil is used. The impact of the amount of the inhaled anaesthetic on awakening from anaesthesia is known from animal and human studies: Eger and Johnson[11] investigated rats that were anaesthetized for 2 h with different volatile anaesthetics and at different multiples of their MAC values. Awakening was typically most rapid with the lowest concentration of the inhaled anaesthetic; this also applies to the results of our study: At the end of surgery, the mean end-tidal desflurane concentration was 3.5 vol% in the fentanyl group, but only 1.9 vol% in the remifentanil group. Similar results were obtained by Smiley and co-workers[12] in patients undergoing elective surgery with desflurane or isoflurane anaesthesia with 0.65× or 1.25×MAC: recovery was faster with the lower anaesthetic concentration.

In addition to the difference in desflurane concentration, the opioid itself will influence the time course of awakening. Glass and colleagues[13] argued that only small amounts of fentanyl or remifentanil are necessary to reduce the MAC, and this also applies to the alveolar concentration of the volatile anaesthetic, at which patients will awake from anaesthesia. Thus, the duration of pharmacodynamic interaction will depend on the duration of the opioid effect; this will clearly be longer with fentanyl than with remifentanil.

A similar anaesthetic technique was proposed by Gerhardt and Grichnik[3] who reported the use of remifentanil in a 60 yr old patient undergoing combined CEA and coronary artery bypass grafting. Their dosage regimen was nearly identical to ours: a remifentanil infusion was titrated to clinical needs and 1/3 MAC (i.e. 0.4 vol%) of isoflurane was added (we used 1/3 MAC of desflurane, i.e. 2 vol%). The authors concluded that remifentanil may retain the haemodynamic stability of an opioid-based anaesthetic technique while allowing for early extubation and neurological examination.

A potential shortcoming of the present study is the question of equivalent levels of anaesthesia in the two groups. The dosage regimens used in this study are comparable to that of other remifentanil-based anaesthesia studies and have been empirically effective. All anaesthetics were delivered by the same experienced anaesthesiologist, who relied on standard clinical signs as described in 'Patients and methods'. Apart from a better reduction in the haemodynamic response to intubation with remifentanil, the haemodynamic characteristics were very similar in the two groups (Table 2). This suggests the equivalence of anaesthesia in the two treatment groups, especially at the end of surgery when the assessment of recovery characteristics was started.

In conclusion, rapid postoperative awakening, quicker recovery and earlier neurological examination suggest that remifentanil–desflurane is a suitable alternative to fentanyl–desflurane as a general anaesthetic for patients undergoing carotid artery surgery.

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Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal

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Recent research has shown that high-frequency, gamma-band electroencephalographic (EEG) oscillations (40–60 Hz) may be an important marker of the conscious state. We compared the ability of the bispectral index (BIS) to distinguish the awake and anaesthetized states during the induction of general anaesthesia with: (i) components of the BIS (BetaRatio, SynchFastSlow); (ii) a new EEG variable—the median frequency of the first time derivative of the EEG signal (SE50d); and (iii) the SE50d derived from an EEG signal that has had the frequencies above 30 Hz removed ($SE50d_{30Hz}$). Two groups of subjects were studied: (i) nine volunteers undergoing a short propofol infusion until loss of response to verbal command, and (ii) 84 patients undergoing routine anaesthesia for a variety of surgical procedures. In the volunteer group, the changes in the BetaRatio and SE50d were comparable with changes in the BIS. The changes in the $SE50d_{30Hz}$ were less consistent. In the patient group, the BIS components were equivalent to the BIS in separating the awake from the surgically anaesthetized states (area under receiver operating curve: BIS 0.95, SE50d 0.95, BetaRatio 0.96). Using the submental electromyogram (EMG) signal to estimate the frontalis EMG (30–47 Hz) signal, the changes in EMG signal were, on average, about one-tenth the magnitude of the EEG. We conclude that: (i) there exist simpler derived EEG variables that are similar in accuracy to the BIS; (ii) it is important to avoid filtering out the EEG frequencies above 30 Hz; and (iii) in most patients the confounding effects of the frontalis EMG on the EEG are minimal.

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By visual inspection there are obvious electroencephalographic (EEG) changes that occur as general anaesthesia is induced in a patient. It is believed that the EEG reflects, to some degree, the level of cortical information processing, and that this changes during the abrupt transition from the state of conscious awareness to that of unconsciousness. Over the years, many putative methods of extracting this information quantitatively from the EEG signal have been proposed.[1 2] These methods usually involve quantifying the increase in low-frequency components of the EEG signal that occurs as anaesthesia deepens. None has been found to be an ideal measure of the depth of anaesthesia. Recent neurophysiological and anaesthetic research has highlighted the importance of the so-called gamma-band EEG oscillations (40–60 Hz) as a marker of the conscious state.[3–7] These are recognized as an irregular, broad-band, high-frequency, low-amplitude (so-called desynchronized) EEG pattern. This pattern is characteristically present when the subject is engaged in specific conscious tasks; it is indicative of the spotlight of attention.[8 9] Experimentally, these gamma rhythms have also been detected at the level of neuronal networks, and have been postulated to be an important part of the process by which the brain binds together sensory input into a conceptual whole that is necessary in the formation of consciousness.[10] Because the spectral power of the scalp EEG signal has a small amplitude at these relatively high frequencies, these contributions to the spectrum have often been ignored when various parameters derived from the EEG power spectrum have been tested as potential monitors of the depth of anaesthesia. One potential problem with using these high-frequency components is that interpretation of the EEG

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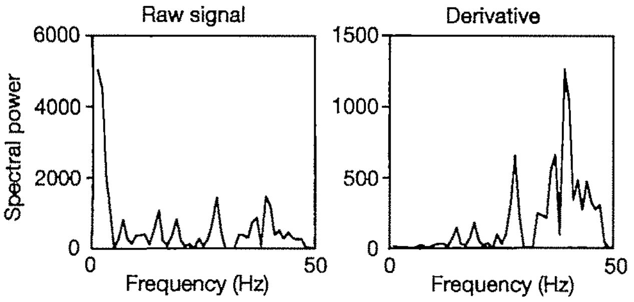

Fig 1 Comparison of typical power spectra of the raw EEG signal with that of the first time-derivative of the same 1 s segment of the EEG signal in an awake patient. The spectral power density of the raw EEG (left) is in units of $(\mu V)^2$ Hz^{-1} and that of the first derivative (right) in units of $(\mu Vs^{-1})^2$ Hz^{-1}. The signal has been digitally band-pass filtered 0.1 to 47 Hz.

signal could be confounded by significant frontalis electromyographic (EMG) spectral power.

However, in recent years the introduction of the bispectral index (BIS) by Aspect Medical Systems (Natick, Massachusetts, USA) has achieved success as an EEG monitor of the conscious state.[11] With the publication of some of the algorithms involved in the derivation of the BIS,[12] it is apparent that one feature that sets this monitor apart from previous monitors is that it recognizes the importance of the higher EEG frequencies (up to 47 Hz) as indicators of the state of consciousness. The details of the calculation and significance of the components of the BIS are discussed in Appendix 1.

There is a large number of possible alternative estimators that could be used to quantify the higher frequencies. In this paper we take a simple approach and use the first time-derivative of the raw EEG signal. Taking the derivative is mathematically equivalent to scaling the EEG signal by its frequency, thus markedly increasing the relative contribution of the higher frequency components and reducing that of the low-frequency components in a linear fashion. Figure 1 compares the power spectrum of the raw EEG signal (left) against that of the first time-derivative of the EEG signal (right).

From our initial discussion we hypothesize that: (i) it is important to include information above 30 Hz when designing an EEG measure of the conscious state, and (ii) simple frequency-related EEG measures may perform comparably with the full BIS in identifying when loss of consciousness occurs. Therefore, in this study we compared the ability of the BIS to differentiate between the awake and anaesthetized states during the induction of anaesthesia, by the use of: (i) components of the BIS (the BetaRatio and the SynchFastSlow); (ii) a new EEG variable—the median frequency of the first time-derivative of the EEG signal (called the SE50d); and (iii) the SE50d, derived from an EEG signal that has had the frequencies above 30 Hz removed (called $SE50d_{30Hz}$). In addition, we have attempted to estimate the degree to which the derived EEG variables (specifically the BetaRatio) may be influenced by changes in the EMG signal that occur as the patient is undergoing general anaesthesia.

Table 1 Clinical details of the patient group

Age (mean (SD))	57 (9) yr	
Sex (female:male)	52:32	
Oral premedication (2 h before induction)	Midazolam (7.5 mg)	*n*=3
Intravenous premedication (5 min before induction)	Midazolam (1–4 mg)	*n*=42
	Fentanyl (50–100 µg)	*n*=67
	Droperidol (1.25 mg)	*n*=5
Induction agents	Propofol (70–200 mg)	*n*=63
	Thiopentone (200–450 mg)	*n*=13
	Etomidate (14–20 mg)	*n*=8
Muscle relaxants	Suxamethonium (100 mg)	*n*=7
	Rocuronium (30–50 mg)	*n*=31

Methods

Clinical procedures

After obtaining permission from the Regional Ethical Committee and informed written consent from participants, we studied EEG changes in two separate groups. The first group (termed the 'volunteer group') consisted of nine fit (ASA I or II) volunteers undergoing light anaesthesia with a slow i.v. infusion of propofol (150 ml h^{-1}) in tightly controlled conditions, as described previously.[13] The EEG data were compared at each of three clinically defined points: (i) start; (ii) loss of consciousness (LOC); (iii) reawakening (responding to verbal command as the effects of the propofol wore off). Encouraged by the results from the volunteer group, we then studied a second, more heterogeneous group (termed the 'patient group'). This group consisted of 84 patients undergoing routine surgery under general anaesthesia. Because we wanted to compare the EEG changes in the varying conditions of routine clinical anaesthesia, the choice of anaesthetic technique was decided entirely on clinical grounds. The clinical anaesthetist was blinded to the EEG monitoring. The various anaesthetic techniques are shown in Table 1.

The patients had no history of neurological disorders. A total of 90 patients (ASA I–III) were recruited but only 84 had complete data sets (two were excluded from the data set because they were unable to respond appropriately to verbal command before induction of anaesthesia, and four had unacceptably high electrode impedances). The clinical stages during the induction of anaesthesia were defined as follows: (i) AWAKE = start time; (ii) LOC = time of loss of consciousness as determined by failure to respond to verbal command ('move your thumb') repeated twice; (iii) LOC60 = LOC + 60 s; and (iv) SURG = start of surgery.

EEG acquisition and analysis

To reduce electrode–skin impedance, the skin over the forehead of each subject was cleaned with an abrasive cleaning fluid (Omniprep; DO Weaver, Aurora, Colorado, USA), and low-impedance electrode paste (Grass EC2 electrode cream; Astro-Med, Warwick, Rhode Island, USA) was placed under disposable adhesive silver–silver chloride electrodes (Meditrace 200; Graphic Controls, Buffalo, NY, USA). We have found previously that, using this arrangement, we are able to obtain electrode impedances similar to, or better than, those obtained with the proprietary disposable EEG electrodes. The EEG was monitored using a bipolar bifrontal montage format (Fp1–Fp2, 10/20 system). The ground electrode was placed at the mid-forehead (Fz) position. In the volunteer group, a second bipolar EEG channel was recorded from the temporoparietal region (T3–P3). In a subset of 30 of the patient group, the second channel consisted of a bipolar pair of electrodes recording the submental EMG signal. The subjects and patients were asked to close their eyes to reduce ocular and blink artefact. An Aspect A-1000 EEG monitor (software version 3.12; Aspect Medical Systems) was used to collect the EEG data. The processed BIS output was recorded at 5 s intervals on a laptop computer, while the raw EEG data were downloaded (sampling frequency 256 samples s^{-1}) onto a second computer for later analysis. Electrode impedance was less than 5000 ohms, and the low- and high-frequency filters were set at 0.5 and 70 Hz with the mains notch filter set at 50 Hz. This filtering applied to the processed output from the Aspect Monitor, but not the raw EEG output. All subsequent processing and analysis were done using purpose-written computer programs in Matlab (Matlab 5.3; Mathworks, Natick, Massachusetts, USA).

SE50d, BetaRatio and SynchFastSlow

The data were processed in 2 s epochs. The signal was low-pass filtered using a phase-preserving 12th-order elliptical digital filter (cutoff frequencies 47–49 Hz, 100 dB roll-off, <2 dB ripple). Then, the signal was processed to reject gross artefacts by excluding epochs in which the absolute magnitude of the signal was greater than 200 µV. The BetaRatio and SynchFastSlow were obtained using the published formula described by Rampil.[12] The exact algorithm for the calculation of the burst suppression ratio (QUAZI Suppression Index) is not in the public domain, and therefore the calculation was not done. In any case, the depth of anaesthesia was such that no burst suppression (as indicated by the Aspect Monitor) was achieved in any patient. The first time-derivative of the EEG signal was then taken and the spectral density of each 2 s epoch obtained (Hanning window). From this, the median frequency of the derivative of the signal (SE50d) could be calculated as the frequency which bisected the area under the derivative-power spectral density curve. The $SE50d_{30Hz}$ was also calculated using a version of the EEG signal that had been additionally digitally low-pass filtered to 30 Hz. This was done because it is common for commercial EEG systems to use this more severe filtering of higher frequencies. The 2 s epochs of all three variables were then smoothed using a moving five-point median window.

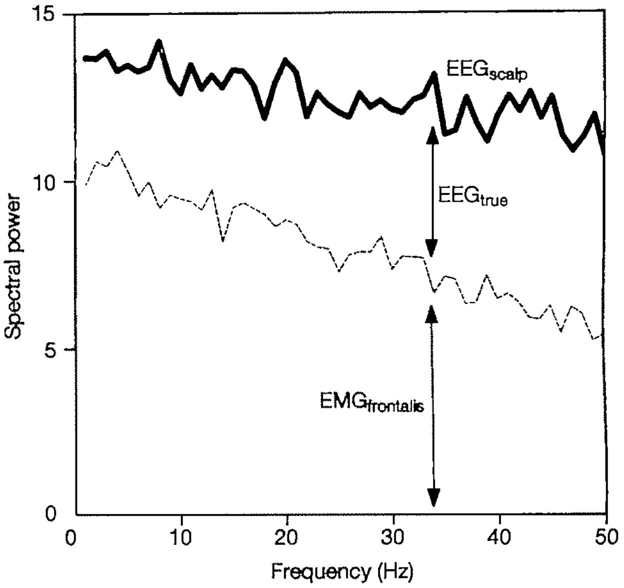

Fig 2 Pictorial representation of how the power spectrum of the observed EEG signal (EEG_{scalp}) consists of the sum of power spectra of the frontalis EMG signal ($EMG_{frontalis}$) and that of the true EEG signal (EEG_{true}).

EMG influence

There has been some criticism that the high-frequency component (30–47 Hz) of the BetaRatio is particularly susceptible to the influence of EMG interference. It is usual to consider the power spectrum of the observed scalp EEG signal (EEG_{scalp}) as the sum of (i) the power spectrum of the true EEG signal (EEG_{true}) and (ii) the power spectrum of the frontalis EMG signal ($EMG_{frontalis}$) (diagrammatically displayed in Fig. 2).

To observe the EEG_{true} signal reliably it would be necessary to have the patient awake and paralysed, which was clearly problematical ethically! However, although we could not measure the $EMG_{frontalis}$ directly, we were able to measure the EMG signal from a bipolar electrode pair sited submentally ($EMG_{submental}$). This pair detects the electrical activity in the muscles of the floor of the mouth and upper neck. This montage is used routinely in sleep monitoring to quantify muscle tone for the evaluation of periods of rapid-eye-movement sleep. An example of the unfiltered $EMG_{submental}$ power spectrum in a conscious patient is shown in Fig. 3. It can be seen that the power spectrum is relatively flat in the frequency range 15–90 Hz (once the 50 Hz mains interference is filtered out).

It is possible to use the spectral power of the $EMG_{submental}$ to estimate the amount of $EMG_{frontalis}$ spectral power that is present in the EMG_{scalp}. The details and assumptions of this method are discussed further in Appendix 2.

Statistical techniques

Unless stated otherwise, data are presented as mean (SD). The changes in the various EEG parameters at each time-point were compared statistically using paired *t*-tests with Bonferroni's correction for multiple comparisons, if the data satisfied normality criteria. In the patient group the data were often skewed, and therefore the Wilcoxon test was used. Receiver operating curve (ROC) analysis was used to compare the ability of the EEG parameters to distinguish the awake and anaesthetized states and to determine the appropriate cutoff values.[14] The anaesthetized state (at the time of surgery) was coded as positive. All the spectral powers were expressed as the 10-base 10 logarithm [i.e. dB relative to 1 $(\mu V)^2\ Hz^{-1}$]. It is important to remember that subtraction of logarithms is equivalent to division, and that a difference of one logarithmic unit is the equivalent of a tenfold difference in absolute value.

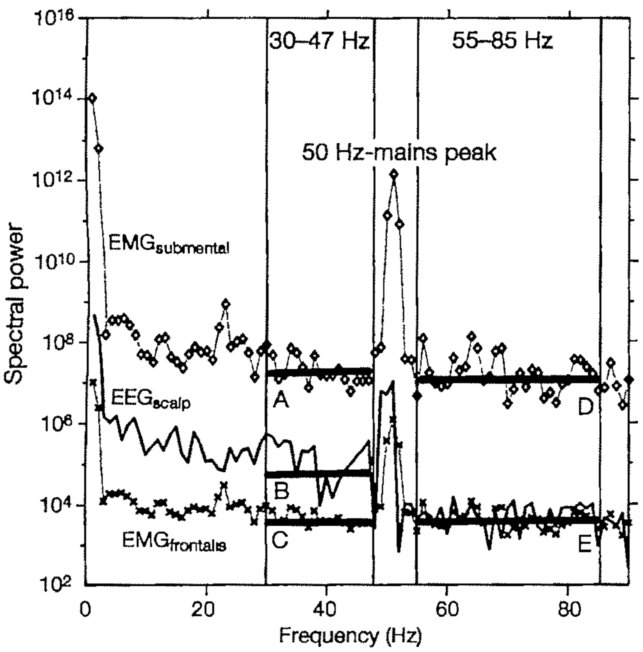

Fig 3 Example of the power spectra of the submental EMG signal and scalp EEG from an awake patient. The $EMG_{frontalis}$ signal cannot be measured directly, but is in fact the same $EMG_{submental}$ signal suitably scaled to give a diagrammatic representation of the various ratios as described in the text. The unit of spectral power is $(\mu V)^2\ Hz^{-1}$.

Results

Volunteer group

Figure 4 shows typical changes of the four indices with time in a single volunteer during and recovering from a propofol infusion. He slowly became more drowsy (the infusion was stopped at the point of loss of consciousness, i.e. at 401 s) and then reawakened (822 s). At the light levels of anaesthesia obtained in this study, both the SE50d and the BetaRatio show relative changes that closely track those of the BIS. The changes in the $SE50d_{30Hz}$ are less pronounced than the SE50d.

We found that the SE50d compared favourably with the BIS in distinguishing the awake and asleep states. As shown in Table 2, in the volunteer group the values of both indices decreased from the starting point to the point of loss of consciousness and then increased at the point of reawaken-

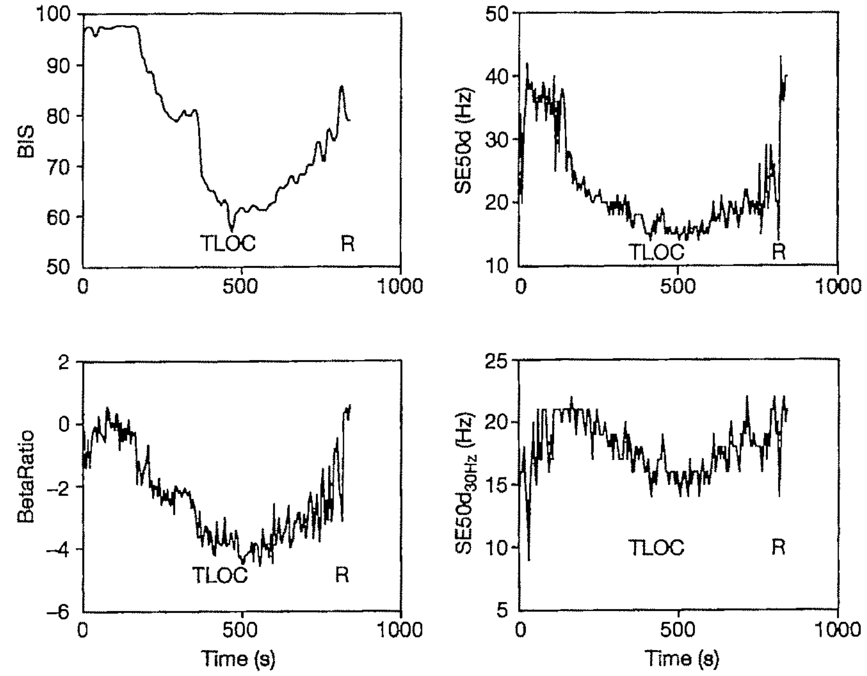

Fig 4 Graphs showing typical changes in EEG indices (BIS, SE50d, $SE50d_{30Hz}$ and BetaRatio) with time for a single volunteer. TLOC is the time of loss of consciousness and R is the time of reawakening.

ing ($P<0.03$). There were no statistically significant differences between data from the frontal and parietal EEG channels. The SE50d demonstrated significant hysteresis ($P=0.0035$) when comparing the values at which subjects awoke with the values when they went to sleep.

Patient group

The clinical details of the patient group are summarized in Table 1. Typical changes of the BIS, SE50d, SynchFastSlow, bispectral power in the bands 0.5–47 and 40–47 Hz, submental EMG power and BetaRatio during induction of anaesthesia in one patient are shown in Fig. 5.

Table 2 Comparison of changes in EEG parameters in the volunteer group (mean (5th to 95th centile))

	BIS	SE50d
Start	96 (94–98)	33 (28–37)
LOC	71 (49–94)	18 (13–27)
Reawakening	78 (61–96)	27(21–35)

It can be seen that the response of the BIS tends to lag behind the other parameters (BetaRatio, SynchFastSlow and SE50d). Whether this lag is due to the pronounced smoothing incorporated in the BIS algorithm or some other cause is not clear.[12] This graph illustrates the decrease in EMG power during induction, and its close correlation with all the other parameters. Figure 5E shows the changes in bispectral power over the whole frequency range (0.5–47 Hz, labelled 'Total') and the high-frequency range (40–47 Hz, labelled 'High'). It demonstrates that the changes in the SynchFastSlow during induction consist of the progressive decrease in high-frequency bispectral power (which closely follows the decline in EMG spectral power) combined with a relatively unchanged, or even increased, total bispectral power at the point of loss of consciousness. The relative changes amongst the different frequency bands of the bispectrum are qualitatively remarkably similar to those seen in the simple power-spectral frequency measures (as quantified by the SE50d and BetaRatio).

A statistical comparison of the changes in the variables is shown in Table 3. All the variables decreased significantly during induction of anaesthesia ($P<0.001$). In all the raw

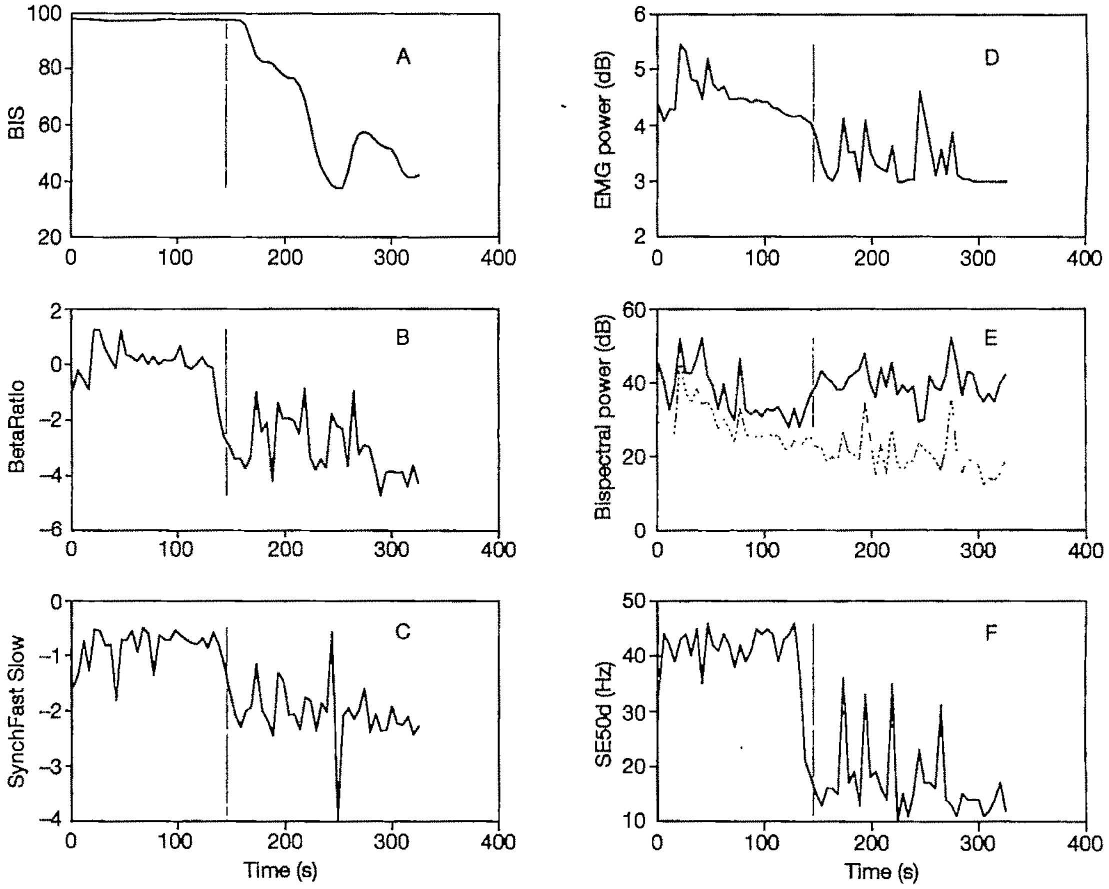

Fig 5 Typical changes in various EEG variables in a single patient during induction of anaesthesia. The vertical dotted line in each graph indicates the time of loss of consciousness. BIS, BetaRatio and SynchFastSlow are dimensionless ratios. The units of EMG power (D) are dB relative to $1(\mu V)^2\ Hz^{-1}$. The total power is the $\log_{10}$ of the volume under the bispectral surface from 0.5 to 47 Hz, and the high power is the logarithm of the volume under the bispectral surface from 40 to 47 Hz. See text for detailed description of the calculation of each variable.

Table 3 Comparison of the EEG variables at various stages of induction of anaesthesia. Values are median (25th to 75th centile). The units of the EMG power are dB relative to $1(\mu V)^2\ Hz^{-1}$. The units of both bispectral powers ('total' is 0.5–47 Hz; 'high' is 40–47 Hz) are dB; the others are unitless ratios. SEF = spectral edge frequency

Variable	Time point			
	AWAKE	LOC	LOC60	SURG
BIS	97 (95 to 98)	94 (87 to 97)	56 (39 to 75)	48 (39 to 67)
EMG_{power} (dB)	4.1 (3.8 to 4.5)	3.4 (3.0 to 3.7)	3.1 (3.0 to 3.3)	3.1 (3.0 to 3.2)
SEF (Hz)	12 (8 to 19)	21 (15 to 24)	13 (7 to 15)	12 (9 to 16)
SE50d (Hz)	40 (36 to 43)	18 (15 to 23)	15 (13 to 18)	15 (13 to 18)
$SE50d_{30Hz}$ (Hz)	20 (15 to 22)	14 (11 to 20)	14 (12 to 16)	14 (12 to 16)
BetaRatio	–0.11 (–0.53 to –0.62)	–2.21 (–2.83 to –1.45)	–2.86 (–3.43 to –2.06)	–2.92 (–3.51 to –2.38)
SynchFastSlow	–0.98 (–1.32 to –0.66)	–1.66 (–1.96 to –1.34)	–1.83 (–2.03 to –1.69)	–1.82 (–2.03 to –1.63)
Total bispectral (dB)	38 (31 to 43)	36 (29 to 42)	34 (27 to 44)	35 (26 to 44)
High bispectral (dB)	28 (20 to 33)	21 (12 to 26)	15 (07 to 25)	16 (9 to 24)

Table 4 Comparison of the predictive power of the three best EEG parameters (distinguishing patients at the start (AWAKE) versus the time of surgery (SURG)). Sensitivity is the proportion of those asleep who are correctly identified as being asleep. Specificity is the proportion of those awake who are correctly identified as awake. PPV is the proportion of patients with a value of the EEG variable less than the cutoff who are correctly diagnosed as being asleep. NPV is the proportion of patients with a value of the EEG parameter less than cutoff who are correctly diagnosed as being awake

Variable (cutoff value)	Sensitivity	Specificity	PPV	NPV
BIS (65)	0.61	0.98	0.97	0.75
SE50d (21)	0.89	0.97	0.97	0.90
BetaRatio (–0.09)	0.89	0.97	0.97	0.90

variables (i.e. other than the BIS), the most marked change occurred between the awake state at the start and the point of loss of consciousness. Using the area (SE) under the ROC curves, the SE50d (0.95 (0.12)), BIS (0.95 (0.12)) and BetaRatio (0.96 (0.12)) showed consistent and equivalent decreases when the values at the time of surgery were compared with those at the start. The SynchFastSlow was slightly less accurate (ROC area = 0.91 (0.12)). In contrast, the $SE50d_{30Hz}$ (0.80 (0.11)) and the 95% spectral edge frequency (0.52 (0.13)) were both significantly worse than the SE50d when comparing the area under ROC curve ($P<0.005$, *t*-test).

At arbitrary but reasonable cutoff points, the predictive power of the three variables was very similar (Table 4): the BIS was somewhat less able to predict the conscious state correctly, i.e. a significant number of patients with BIS>65 (who would be predicted to be awake) were actually asleep, indicating a greater overlap in awake versus asleep values by the BIS. If BIS of less than 57, a SE50d of less than 17 or a BetaRatio of less than –0.70 was used as the cutoff value, all three indices would achieve 100% positive predictive value.

EMG influence (n=30)

The interpretation of the EMG influence was not straightforward. During induction of anaesthesia, the spectral power of the $EMG_{submental}$ did not change significantly in the lower frequencies (1–20 Hz), but did decrease significantly ($P<0.001$) in the higher frequency range (20–47 Hz). As may be expected from this, the slope of the $EMG_{submental}$ power spectrum tended to increase with increasing depth of anaesthesia in a fashion that was similar to but less marked than that observed in the EEG (as estimated by the BetaRatio, for example).

When estimating the proportion of the EEG signal that was contaminated by the frontalis EMG signal, we used the 30–47 Hz frequency band, because that is the high-frequency component of the BetaRatio. Overall, the median (25th to 75th centile) of the ratio of $EEG_{scalp(30\text{–}47Hz)}$: $EMG_{frontalis(30\text{–}47hz)}$ was 12.6 (2.1–21) dB. This means that, on average, the EEG signal in the 30–47 Hz (i.e. low gamma) frequency band was more than eighteen ($=10^{1.26}$) times the magnitude of the EMG signal. However, the difference was more marked in the AWAKE state, for which the median ratio was 21.1 (14.7–27.5) dB. This corresponds to the EEG being over 100 times more powerful than the EMG in the gamma band. However, it must be noted that in the lowest decile of the patients the ratio was negative (i.e. the EMG power was greater than the EEG power). This indicates that, in some patients at least, there are inaccuracies in the assumptions used to derive the frontalis EMG amplitude.

Discussion

There are three main results from this study: (i) that there exist simpler (non-bispectral) derived EEG variables that are similar in accuracy to the BIS in separating the awake from the surgically anaesthetized states; (ii) that, when detecting loss of consciousness, it is very important to avoid filtering out the frequencies above 30 Hz; and (iii) the changes in the power spectrum of EMG during induction are similar to the changes seen in the EEG, but are about ten times less in magnitude on average.

Compared with the BIS in our study, these alternative EEG indices are at an additional disadvantage because there was minimal artefact rejection in their preprocessing compared with the sophisticated artefact management used in the derivation of the BIS.[12] All predictive results need further prospective testing on an independent group before they can be recommended for routine clinical use. It must also be emphasized that the EEG parameters were evaluated during the induction of general anaesthesia. The changes that may occur during reawakening at the end of anaesthesia may differ.

It seems plausible that the improved performance of the SE50d (over the spectral edge frequency and the $\text{SE50d}_{30\text{Hz}}$) is due to: (i) the use of the first derivative, which has the effect of filtering out the fluctuating low-frequency artefact noise which, episodically, can dominate the true low-amplitude, high-frequency EEG power spectrum in the awake patient; and (ii) the fact that the SE50d emphasizes the importance of the desynchronized gamma rhythms, which are associated with the EEG of a subject in the attentive conscious state. The BetaRatio and the SE50d are similar in that they quantify the dominant EEG frequencies within a constrained frequency band. This includes the lower part of the gamma band and excludes the variable, dominant effects in the low frequencies (<10 Hz).

Schnider and colleagues, using the EEG as a monitor of propofol effect, have developed a variable called the semilinear canonical coefficient.[15] In simple terms this is a development of the statistical method of canonical regression, which, by an iterative method, automatically derives the best combination of weights for each frequency bin to describe the changes in the EEG signal during the transition from the alert state to anaesthesia. The non-linear link function is required to allow for the variable biphasic EEG response that occurs in the stage of light anaesthesia. In keeping with traditional practice, Schnider and colleagues used low-pass filtering of the EEG signal to exclude frequencies above 30 Hz. The diagrams of changes in the semilinear canonical coefficient during induction of anaesthesia in their paper (Fig. 3) are very similar to that of the $\text{SE50d}_{30\text{ Hz}}$ in our paper (Fig. 4), showing a biphasic response. We suggest that this biphasic response may be attenuated or eliminated by the inclusion of higher frequencies in the analysed EEG signal.

There has been a number of studies using the auditory evoked steady-state response as a measure of depth of anaesthesia.[16] [17] These studies have shown a good correlation between increasing anaesthetic concentrations and attenuation of the auditory evoked steady-state response.[18] Although the exact neurophysiological correlation between evoked (25 ms) 40 Hz activity and spontaneous EEG gamma-band activity is not entirely clear, there appears to be significant convergence: both are found to be relatively accurate indicators of the alert state.[19] It is of interest that, in a study by Schraag,[20] the area under the ROC curve (distinguishing the unconscious and conscious states) for the BIS (0.92) and their auditory evoked potential index (0.97) were very similar to the area under the ROC curves in our study. A simple estimator of the auditory response (the 'auditory evoked potential index') quantifies the response by summing the absolute magnitude of the first time-derivative of the signal, a procedure similar in some respects to the derivation of the SE50d.

The influence of changes in the frontalis EMG on the observed scalp EEG is problematical. Using our results, it would seem that, statistically, in about 90% of patients the EMG signal is a minor component of the observed scalp EEG signal. There is the important proviso that these conclusions are based on information obtained indirectly from the $\text{EMG}_{\text{submental}}$ and not directly from the (unmeasurable) $\text{EMG}_{\text{frontalis}}$. We have made the unproven assumption that, at least in the higher frequency ranges (>20 Hz), the slope of the power spectrum of the $\text{EMG}_{\text{frontalis}}$ was similar to that observed in $\text{EEG}_{\text{submental}}$. However, this problem is probably not clinically harmful, and is biased towards preventing intraoperative awareness in both possible scenarios. In most cases the effect of a high EMG spectral power is to flatten the BetaRatio, i.e. to make the patient appear more awake than he really is, and thus the anaesthetist would be tending to err towards increasing the amount of anaesthetic agent. Conversely, the $\text{EMG}_{\text{frontalis}}$ may have a very steep spectral slope (corresponding to an EMG BetaRatio of perhaps –3.00) caused by noise in the form of an excessive low-frequency EMG component of the scalp EEG signal, which would suggest that the patient is asleep when in fact he is awake. In this case, if the patient had that amount of muscle activity he would be able to forcefully indicate his conscious state to the surgeon! It is fortunate that all EEG indices tend to become more reliable in the presence of muscle relaxation (as long as this effect is taken into account when setting the thresholds of EEG parameters used for determining awareness).

One of the main criticisms of the BIS has been that it is derived empirically and not based on theory and neurophysiological facts. This study may go some way towards clarifying why the BIS is effective. As has been previously stated,[12] the BetaRatio is the important component of the BIS at light levels of anaesthesia. The success of this subcomponent in tracking the patient's level of consciousness during induction of anaesthesia seems to indicate that, if the goal is to decide if the patient is aware or not, then the dominant frequency of the 'desynchronized' oscillation is the important EEG feature. This phenomenon of blocking of the gamma rhythms is a feature of the commonly used

GABAergic general anaesthetic agents, and is much less marked with excitatory anaesthetic agents such as nitrous oxide or ketamine, which tend to maintain the gamma-band EEG activity.[21 22] This would explain why the BIS is not very sensitive when used during sedation with nitrous oxide.[23 24] The utility of the SE50d and BetaRatio with nitrous oxide is unknown.

Appendix 1

The two important subcomponents of the BIS—the BetaRatio and the SynchFastSlow—both estimate the importance of higher frequencies relative to the total signal. The BetaRatio is the logarithm of the ratio of the EEG spectral power in the 30–47 Hz band to the EEG spectral power in the 11–20 Hz band:

$$\text{BetaRatio} = \log_{10} [\text{spectral power}_{(30\text{–}47\ \text{Hz})} / \text{spectral power}_{(11\text{–}20\ \text{Hz})}].$$

The SynchFastSlow is the logarithm of the ratio of the bispectral power in the waveband 40–47 Hz to that in the band 0.5–47 Hz:

$$\text{SynchFastSlow} = \log_{10}[\text{bispectral power}_{(40\text{–}47\text{Hz})} / \text{bispectral power}_{(0.5\text{–}47\text{Hz})}].$$

It may be surmised that the success of the BIS may be due, in large part, to the emphasis on these higher frequencies extending into the gamma band. Although the bispectral index (BIS) is widely used as a monitor of the depth of anaesthesia, it has some disadvantages: (i) it is an empirically derived black box, with a complex non-linear algorithm that is difficult to relate to electrophysiological changes; (ii) the exact point at which individual patients lose consciousness occurs over a wide range of BIS values; (iii) it has a significant time lag, thus precluding individual titration to effect; and (iv) it does not reliably warn of impending arousal.

Almost all the published work on the higher-order spectra of the EEG signal in anaesthesia describes the changes in only the processed output of the Aspect Monitor: the BIS. Changes in the actual raw bicoherence and bispectrum of the EEG signal during natural sleep and epileptic seizures have been analysed by Bullock and colleagues.[25] Because the basis of the algorithm for calculating the BIS is not freely available, it is difficult to interpret the observed changes in terms of known neurophysiological processes. To understand the BIS fully, it is necessary to dissect it into its various subcomponents as far as possible. The theoretical basis of the bispectrum of the EEG signal is difficult to visualize intuitively. It has been claimed that a significant bispectral power is indicative of non-linear (quadratic) interfrequency phase coupling.[26] Strictly, this interpretation implies interactions among regular stationary cortical oscillators. It may be more realistic to consider the EEG as a stochastic (random) signal. In this case, the bispectral power may be better interpreted statistically as an estimate of the degree to which the signal is non-Gaussian, specifically its skewness.[27 28] Measurement noise and the EMG signal are both approximately Gaussian in distribution, and thus should not appear in the bispectrum. Therefore, it is conceivable that the bispectral techniques are effective because they are effectively reducing the influence of unwanted extra-EEG noise rather than revealing information about the degree of neurological integration. Unfortunately, the interpretation of the bispectrum is further complicated by the fact that even a truly Gaussian time series will have a non-zero bicoherence, because the bispectrum is a biased estimator, being distributed approximately as a χ^2 distribution.[29] Thus, it could be argued that the inclusion of complex bispectral measures is not important as long as the changes in high-frequency content are included in whatever EEG variable is chosen. If this is true, we could expect that similar information could be obtained without the necessity of using higher-order spectral techniques, by the use of a simpler, cut-down component of the BIS—the BetaRatio.

Appendix 2

There are two facts that make it possible to derive indirectly some (imperfect) information about the power spectrum of $\text{EMG}_{\text{frontalis}}$ and hence EEG_{true}. First, we can measure the $\text{EMG}_{\text{submental}}$ directly using a separate bipolar montage, giving an almost pure EMG signal. Secondly, the EEG content in the frontalis spectrum is negligible above 55 Hz. Thus, we can use the $\text{EMG}_{\text{submental}}$ to estimate the changes in the shape and slope of the EMG spectrum during induction of anaesthesia. We can then combine this information with the actual power of the $\text{EEG}_{\text{scalp}}$ (equivalent to purely $\text{EMG}_{\text{frontalis}}$) in the frequency band 55–85 Hz to estimate what proportion of the total scalp 30–47 Hz power is attributable to $\text{EMG}_{\text{frontalis}}$. This relies on the assumption that the slopes of the power spectra of $\text{EMG}_{\text{frontalis}}$ and $\text{EMG}_{\text{submental}}$ are similar (Fig. 3). The frontalis and submental EMG signals may both be affected independently by intermittent phenomena, such as voluntary local swallowing movements ($\text{EMG}_{\text{submental}}$), episodic brow wrinkling and eye movements ($\text{EMG}_{\text{frontalis}}$). Intuitively, it seems likely that the low-frequency components (<11 Hz) of the two EMG power spectra would often be uncorrelated, and we therefore ignored them. Conversely, the higher frequencies (gamma band) are more likely to reflect ongoing muscular tone and to be less sensitive to differences in voluntary movements between the forehead and the throat. The derivation of the mathematical formulae used to estimate the relative 30–47 Hz power is as follows. We assume that the $\text{EMG}_{\text{submental}}$ power spectrum behaves as an approximate scaled replica of the (unknown) $\text{EMG}_{\text{frontalis}}$ spectrum for frequencies higher than 30 Hz.

The ratio of submental to frontalis EMG power in the 30–47 Hz band equals the ratio in the 55–85 Hz band (using the symbols shown in Fig. 3):

$$A/C = D/E \qquad (1)$$

where A is the 30–47 Hz submental power ($EMG_{submental(30–47Hz)}$), C is the 30–47 Hz frontalis power ($EMG_{frontalis(30–47Hz)}$) (unknown), D is the 55–85 Hz submental power ($EMG_{submental(55–85Hz)}$) and E is the 55–85 Hz frontalis power ($EMG_{frontalis(55–85Hz)}$). C is unknown but can be calculated from equation (1).

Actually we want to estimate the ratio B/C, where B is the 30–47 Hz total EEG power ($EEG_{scalp(30–47Hz)}$).

From equation (1),

$$B/C = (B{\cdot}D)/(A{\cdot}E) \qquad (3)$$

Taking logs, and expressing in decibels,

$$10\log_{10}(B/C) = 10\log_{10}(B) + 10\log_{10}(D) - 10\log_{10}(A) - 10\log_{10}(E).$$

This will allow us to quantify the extent to which the total observed EEG power in the 30–47 Hz band ($EEG_{scalp(30–47Hz)}$) has been contaminated by frontalis EMG power. All the terms on the right-hand side of the equation are measurable experimentally.

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Effects of different concentrations of sevoflurane and desflurane on subcortical somatosensory evoked responses in anaesthetized, non-stimulated patients

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Twenty-four patients were recruited and given either sevoflurane or desflurane as their sole anaesthetic. Each patient was given sequentially increasing or decreasing doses at 0.5 MAC intervals, and the median nerve somatosensory evoked response recorded after an equilibration at each concentration. The N_{20}-P_{25} and P_{25}-N_{35} amplitudes decreased with increasing agent concentration. However, for both agents the P_{15}-N_{20} amplitude response was quadratic in shape. The peak inflection points were at 3.2% for sevoflurane and 4.9% for desflurane. There were no differences between the ascending and descending groups. This increase in activity in the midbrain at 'surgical' end-tidal anaesthetic concentrations suggests more complex neuroelectrical responses to anaesthesia than simple global suppression.

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Keywords: anaesthetics volatile, desflurane; anaesthetics volatile, sevoflurane; brain, evoked responses

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The somatosensory evoked response (SER) is a stimulus related potential of the central nervous system derived from the electroencephalograph (EEG). It is routinely used in spinal and head and neck surgery to assess perioperatively the functional integrity of ascending pathways during surgery (see Fig. 1). Increasing suppression of cortical SER as indicated by decreasing wave amplitude and increasing latency with increasing anaesthesia is widely reported during anaesthesia with volatile anaesthetics, barbiturates, benzodiazepines and opioids.[1–5] This effect has also been noted in subcortical waves but these waves are said to be more resistant to anaesthetic suppression.[6]

We studied the effects of different concentrations of desflurane and sevoflurane on early SER waves. The amplitudes P_{15}-N_{20}, N_{20}-P_{25}, and P_{25}-N_{35} were studied. These amplitudes are thought to represent activity in the pontothalamic, thalamic and thalamic/primary sensory cortex portions of the pathway, respectively,[7–9] although the exact site of the generators is a subject for ongoing debate in the EEG literature. Our patients were not undergoing surgery during data acquisition and were ventilated using a laryngeal mask airway (LMA™) to minimize external stimuli.

Patients and methods

After local ethics committee approval 24 patients gave written, informed consent and were recruited to the study. All were ASA I and II and attending our hospital for elective surgery. No premedication was used. On arrival in the anaesthetic room full non-invasive monitoring was applied and intravenous (i.v.) access obtained. Inhalational induction of anaesthesia was performed with either sevoflurane or desflurane. Once the subjects were anaesthetized muscle relaxation was obtained with vecuronium 0.1 mg kg^{-1} and a LMA of appropriate size sited. Patients were then ventilated to normocapnia using oxygen and the relevant agent only. End-tidal carbon dioxide and volatile agent were measured continuously with a calibrated Datex™ Capnomac Ultima™ monitor (Datex, Helsinki, Finland).

Patients were randomized to receive five sequential concentrations of sevoflurane or desflurane. To correct for possible time trends and to ensure adequate equilibration at each anaesthetic level patients were also randomized to receive the agent in an ascending or descending order. The levels were set at approximately 0.5 MAC intervals, and each end-tidal concentration was maintained for at least 10 min to allow equilibration prior to data collection. At the

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end of data collection the patients were transferred to the operating theatre and the operation started.

Data collection

The median nerve was stimulated at the wrist with an electrical pulse delivered at a rate of 2.2 s^{-1} and at an intensity adjusted to just above the motor threshold (11–13 mA). The SER was derived from the electroencephalogram, and recorded using silver/silver chloride electrodes attached at Fz and C_3. SER data were collected over the last 2.6 min of each agent concentration period (356 EEG sweeps) on a system developed in our unit.[10] These were averaged and analysed offline. The amplitudes P_{15}-N_{20}, N_{20}-P_{25} and P_{25}-N_{35} were measured at each anaesthetic concentration.

Results

Patient subgroups were similar in terms of age, sex and weight (see Table 1).

The SER amplitudes were plotted against end-tidal agent concentration for sevoflurane and desflurane, and are shown in Figs 2 and 3. The data from the ascending and descending subgroups for each agent were compared using a two sample *t*-test to assess for differences, and in each case were not significantly different (sevoflurane P=0.37; desflurane P=0.98).

For both agents a dose related decrease in amplitude with increasing anaesthetic end-tidal concentration was seen in the N_{20}-P_{25} and P_{25}-N_{35} amplitudes. The P_{15}-N_{20} amplitude for both agents increased with increasing agent concentration before falling – a quadratic curve. Quadratic regression curves fitted each patient data-set significantly better than a straight line (P<0.001 in both cases). The inflexion point for these curves were at 3.2% (95% confidence intervals 2.9–3.4%) for sevoflurane, and 4.9% (95% confidence intervals 3.1–6.8%) for desflurane. The evoked potentials for one patient in the sevoflurane group are shown (see Fig. 4; only four of the five concentration curves are shown for clarity).

The mean inflexion points were compared for the two agents in terms of MAC, using 1 MAC=sevoflurane 2%=desflurane 6%. There was a significant difference

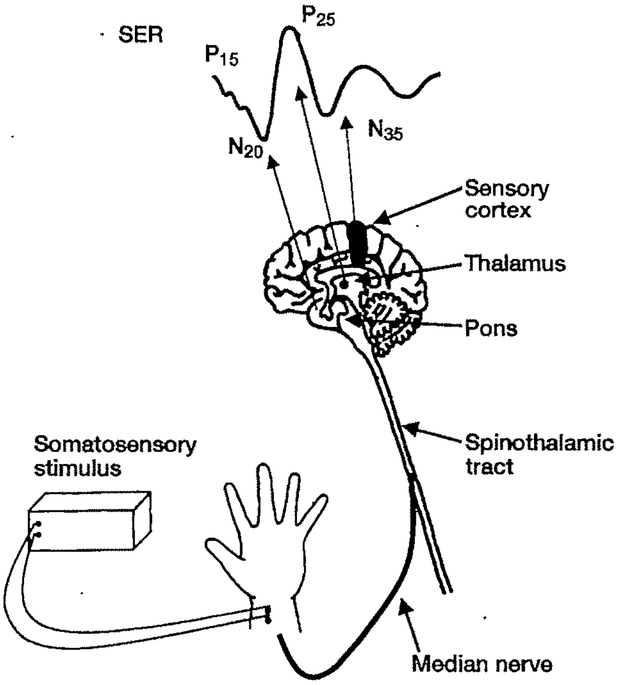
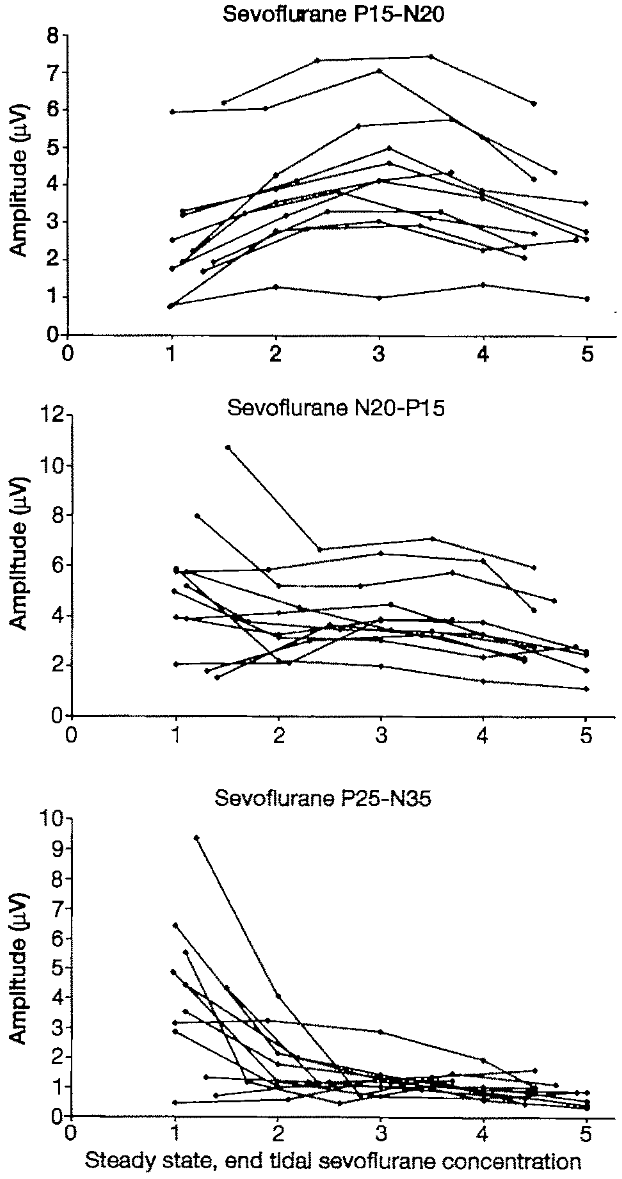


Fig 1 The pathway of the early SER waveform and the associated generator areas.


Sevoflurane P15-N20

Sevoflurane N20-P15

Sevoflurane P25-N35

Fig 2 Subject curves showing end tidal sevoflurane concentration against the potential difference for the SER amplitudes P_{15}-N_{20}, N_{20}-P_{25} and P_{25}-N_{32}.

Table 1 Subject characteristics by subgroupings. Data for age and weight is presented as mean (range)

	Sevoflurane subjects		**Desflurane subjects**	
	Ascending	**Descending**	**Ascending**	**Descending**
Sex (M:F)	4:2	4:2	4:2	3:3
Age (yr, range)	42 (21–64)	43 (27–58)	37 (20–50)	41 (35–56)
Weight (kg)	65 (51–92)	68 (59–87)	62 (55–83)	71 (62–95)

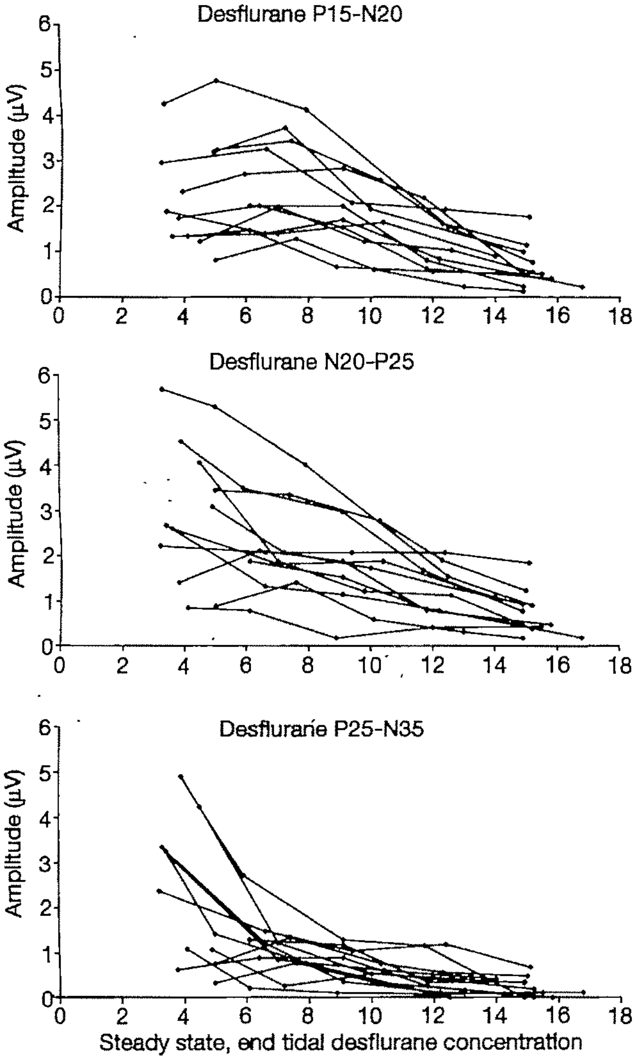


Fig 3 Subject curves showing end tidal desflurane concentration against the potential difference for the SER amplitudes P_{15}-N_{20}, N_{20}-P_{25} and P_{25}-N_{32}.

between the two agents (inflexion point for sevoflurane 1.5 MAC, desflurane 0.8 MAC, $P<0.01$).

Discussion

Increasing concentrations of anaesthetic agent, both inhaled and i.v., are widely recognized to cause suppression of central nervous system electrical activity as measured by the EEG and EEG derived variables (e.g. evoked responses and the Bispectral Index).[6 11 12] Subcortical evoked response amplitudes are known to be relatively resistant to the effects of anaesthesia. This is one of the reasons that later, cortical mid latency evoked response amplitudes are commonly used for depth of anaesthesia assessment.

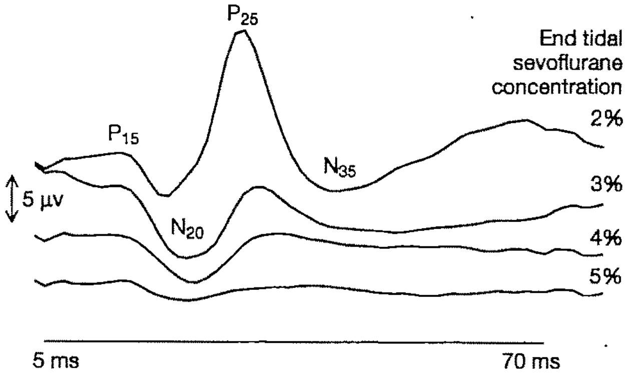


Fig 4 Sample traces of one subject. The increase in P_{15}-N_{20} amplitude is clearly seen as the other amplitudes decrease.

Increases in P_{15}-N_{20} amplitude after bolus doses of etomidate have been reported,[13–15] during surgery with non standardized and varied doses of anaesthetic agents. This may represent the same phenomenon but the presence of other agents and variable surgical stimuli may be confounding. The technique was recommended to augment SER signals during surgery. Jantti and colleagues also reported an increase in this amplitude during sevoflurane anaesthesia.[16] They recorded data at burst suppression (1.5–2.5 MAC sevoflurane) rather than at specific anaesthetic end-tidal concentrations and found similar potentiation of this amplitude, but did not report amplitude changes over a range of concentrations in each subject.

There are several plausible reasons for this increase. The site of increased activity cannot be localized anatomically from these data, because the amplitude represents the activity attributable to the median nerve stimulus at the stated time after stimulation rather than at a known site in the midbrain. However, it is widely held that the generators of the P_{15}-N_{20} amplitude are in the pontothalamic area.

Increasing electrical activity in the midbrain could be caused by a direct, anaesthetic mediated increase in inhibitory postsynaptic potential (IPSP) generation, or a more generalized interruption of intercellular communication. One interesting possibility involves recent *in vitro* work by Traub, Whittington and others, which shows that anaesthetic and analgesic drugs disrupt gamma frequency oscillations originating in the hippocampus and midbrain.[17 18] These high-frequency signals are thought to represent the co-ordination of sensory input analysis between anatomically discrete areas of the brain. When disrupted, the gamma frequency output increases. This is thought to be due to anaesthetic and analgesic drugs decreasing gamma-aminobutyric acid (GABA) type A receptor mediated inhibition of excitatory and inhibitory interneurons.[19] This increase in gamma signal could explain the increased electrical activity in the midbrain seen up to the point where direct pathway effects (burst suppression of the EEG) are seen, causing the fall in voltage at higher anaesthetic concentrations. It also may explain the increasing sensory detachment leading to and including the state of anaesthesia. However there is no human *in vivo* evidence to support or refute this at present.

The peak values at the points of inflexion of sevoflurane and desflurane differ significantly when compared using MAC values. These data must be interpreted carefully as the desflurane group peak value is not central in the data points measured. However, MAC is primarily a motor descriptor and the SER relies on a purely sensory pathway. Thus, in the same way as different volatile anaesthetics may have different vasodilator effects at equal MAC concentrations, their effects on neuronal transmission may differ.

In conclusion, we have found that the subcortical SER does not respond in a uniform way to increasing anaesthetic concentration. The N_{20}-P_{25} and P_{25}-N_{35} amplitudes decrease with increasing anaesthetic concentration, but the P_{15}-N_{20} wave is potentiated at clinically relevant end tidal sevoflurane and desflurane concentrations.

Further work is needed to more closely analyse the anatomical site, if any, of this increased signal.

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Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery

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Conventional methodology to investigate cognitive impairment after coronary artery bypass graft (CABG) surgery leaves unclear the potential for pre-existing cognitive deficits to influence outcome. Individuals with pre-existing deficits may be more vulnerable to the effects of CABG, hence biasing the results of a typical prospective trial if account is not taken of their state. The present study examined the effect of pre-existing cognitive impairment upon cognitive outcome in 81 patients undergoing CABG. Patients performed the Stroop Neuropsychological Screening Test and other psychometric assessments prior to and at 6 days and 6 months after CABG. Those with pre-existing cognitive deficits were significantly more likely to display impairment at 6-day and 6-month follow-ups than were those without pre-existing deficits. Greater age and lower pre-morbid intelligence were also significant predictors of post-CABG deficit, confirming earlier findings. The results imply both that pre-existing cognitive impairments may render patients more vulnerable to post-operative deficits and that, in the absence of such pre-existing impairments, CABG surgery does not inevitably lead to later deficits. The study also replicated previous findings showing a similar influence of pre-existing depression upon emotional state after CABG. Overall, the results confirm the importance both of a patient's pre-existing cognitive and emotional states, and the methodology to assess them, in influencing outcome after cardiac surgery and the conclusions to be drawn as to the supposed adverse effects of the procedure.

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Keywords: surgery, cardiovascular; complications, cognitive impairment; complications, depression

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The recent review by Arrowsmith and colleagues[1] follows earlier authors in addressing the significant issues concerning the assessment of cognitive deficits following cardiac surgery and anaesthesia.[2–4] The present research illustrates the importance of detecting cognitive deficits which may exist prior to coronary artery bypass graft (CABG) surgery in order to understand more fully the effects of the procedure upon outcome. Central to the method is the use of tasks that can define absolute, rather than relative, cognitive impairment.

The assessment of intellectual deficits after CABG frequently employs performance tests which lack performance norms and hence cannot establish in absolute terms whether a patient is 'impaired'. Impairment can only be established in relative terms from differences in performance before and after surgery (either statistically different or some arbitrary difference between pre- and post-scores such as 1 SD, or 20% decline, etc.). As the approach neglects whether a patient may have been cognitively impaired prior to the procedure, two difficulties arise. First, as patients with pre-existing impairments may be more vulnerable to the adverse effects of CABG, their inclusion in a sample may then inflate the apparent risk attached to the procedure. Conversely, patients who are already impaired may be performing so poorly that a 'floor effect' occurs whereby there is little scope for their performance to become worse; hence giving the misleading impression that the procedure has little adverse effect.

Such difficulties may be addressed by using tests that have norms to establish absolute impairment and thus detect

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pre-existing deficits. The present study makes such an assessment by using the Stroop Neuropsychological Screening Test[5] which has age-related impairment norms to define absolute impairment. The Stroop assesses attention and the ability to resist distraction, and is sensitive to impairment as a result of mild brain damage and to the subtle changes seen in mild to moderate dementia.[6] Performance on the Stroop prior to CABG has already been shown to be predictive of post-operative outcome.[7] However, critically, the investigators did not take account of whether the pre-operative performance was indicative of absolute impairment. Other studies which have employed the Stroop to investigate both CABG-related impairment[8–10] and post-anaesthetic recovery[11] have confirmed the sensitivity of the task to change from pre- to post-operative state but, again, without accounting for pre-operative impairment.

The potential importance of accounting for the patient's pre-existing cognitive state in interpreting post-CABG deficits is not speculative but is confirmed by parallel research concerning the effects of CABG upon emotional state. Whilst the reported significant increases in depression after CABG have commonly been assumed to be a direct consequence of the procedure, research has shown that the presence of pre-existing depression is a significant determinant of the post-CABG state: patients who are not depressed beforehand are at substantially lower risk.[12–15]

The methodology of the present study involves assessment of both absolute cognitive impairment and presence of depression prior to CABG, hence clarifying whether pre-existing impairments predict post-operative outcome, and replicating the existing results concerning depression and CABG outcome.

Methods

Patients and procedure

Following approval of the study by the Ethics Committee of the Western Infirmary, Glasgow, 120 patients (92 men, 28 women; 77:23%) undergoing coronary artery bypass graft (CABG) surgery gave informed consent to participate. The standard anaesthetic regimen was adapted as necessary according to the patient's physical state and cardiac drug therapy. Patients were premedicated with temazepam or lorazepam orally the night before, and on the morning of surgery. After pre-oxygenation and establishing venous and arterial access, anaesthesia was induced with propofol and fentanyl. Tracheal intubation was facilitated, and neuromuscular blockade maintained by bolus doses of pancuronium. The lungs were inflated with at least 30% oxygen in nitrous oxide with varying doses of isoflurane. During cardiopulmonary bypass, additional fentanyl was given and a propofol infusion used. The bypass system, using a membrane oxygenator, was regularly adjusted according to measurements of pH and $P\text{CO}_2$. The patients were cooled to core temperatures between 28 and 32°C, and the heart arrested using St Thomas's cardioplegia solution. Infusions of nitroglycerine and dopamine were used to support the heart and circulation as required. The patients were transferred to a cardiac intensive care unit for recovery, the majority being returned to the ward the next day.

Psychometric assessment

Patients were assessed 3 days before, and 6 days and 6 months after CABG. The Stroop Neuropsychological Screening Test[5] consists of a sheet presenting a list of 112 colour names printed in incongruous colours (e.g. the word 'blue' printed in green ink). The subject was required to read through the list as quickly as possible, reading out the name of the colour in which the word is printed. The interference effect produced by the incongruity of the word name and the colour of its presentation renders the task very demanding of attention and concentration. The score is the number of words read correctly in 2 min. The task norms allow an individual's score to be categorized as indicative of likely brain damage as a function of their age. Depression was assessed with the self-report Beck Depression Inventory[16] using the conventional criterion of a score $\geqslant 9$ as indicative of depression. Years of education are known to have a protective function from the adverse effects of CABG, [17] hence pre-morbid intellectual status was assessed prior to CABG with the National Adult Reading Test (NART).[18] Personality characteristics of extroversion and neuroticism can predict post-surgical outcome[19] and were assessed prior to CABG by the Eysenck Personality Questionnaire.[20]

Statistical analysis was conducted with Minitab version 12 via Windows 95 on a Viglen Contender PC.

Results

Eighty-one of the 120 patients completed the assessments at all three periods (64 men, 17 women; 79:21%, the proportions being almost identical to the original full sample hence indicating equivalent attrition as a function of gender). The mean ages for men and women (SD; range) were 59.4 (8.7; 38–76) and 62.4 (10.0; 37–73) yr respectively. Because of the very small proportion of women participating in the study, the factor of gender is not considered further in the analysis. The mean NART error score of 15.2 (SD 6.85) corresponded to an average IQ of 111.[5]

Table 1 shows the number and percentage of patients suffering cognitive impairment at 6 days or 6 months follow-up, or at both follow-ups, as a function of their pre-CABG state. Prior to CABG, 13 (16%) patients had pre-existing impairment. Postoperatively, 11 (85%) of the latter patients were impaired at 6 days, a total comprising six (46%) who were impaired only at 6 days and five (39%) who were impaired at 6 days and remained so at 6 months. In contrast, of the 68 (84%) who were not impaired prior to the

Table 1 The number and percentage of patients suffering cognitive impairment and depression as assessed by Stroop Neuropsychological Screening Test and Beck Depression Inventory before and after coronary artery bypass graft surgery. Mean Stroop performance before and after surgery is shown in the lower panel of the table (SD in parentheses)

Impairment	**Pre-operative status**	**Post-operative status**		
		Impaired at 6 days only	**Impaired at 6 days and 6 months**	**Impaired at 6 months only**
Impaired	13 (16%)	6 (46%)	5 (39%)	0
Unimpaired	68 (84%)	8 (12%)	1 (2%)	0
Depression	**Pre-operative status**	**Post-operative status**		
		Depressed at 6 days only	**Depressed at 6 days and 6 months**	**Depressed at 6 months only**
Depressed	23 (28%)	9 (39%)	9 (39%)	3 (13%)
Not Depressed	58 (72%)	6 (10%)	2 (4%)	3 (5%)
Mean Stroop performance	**Pre-operative**	**6 days**	**6 months**	
	85.5 (19.6)	80.4 (22.0)	93.3 (17.8)	

procedure, a total of nine (14%) became impaired at 6 days, these being eight (12%) who were impaired only at 6 days and one (2%) who was impaired at both follow-ups. By contrasting the proportion of patients who were impaired with those unimpaired before CABG and at follow-up, the presence of pre-CABG impairment was found to be a significant predictor of the post-procedure state (Fisher's exact test, both $P<0.001$). There was no evidence of late-onset impairment: no patient was impaired at 6 months without having previously been impaired.

Table 1 also shows that depression as a function of the pre-CABG state follows an identical pattern to that for impairment. Of the 23 (28%) patients who reported pre-operative depression, a total of 18 (78%) continued to be depressed at 6 days follow-up, nine (39%) of these being depressed only at 6 days and nine (39%) being depressed at both follow-up periods. Of the 58 (72%) who were not depressed prior to CABG, a total of eight (14%) reported depression at 6 days follow-up, six (10%) of these being depressed only at 6 days and two (4%) being depressed at both follow-ups. By contrasting the proportions of patients who were depressed with those who were not depressed before CABG and at the subsequent two follow-ups, the presence of pre-CABG depression was found to be a significant predictor of the post-procedure state (chi-squared, both $P<0.001$). Late-onset depression at 6 months was evident in 6 patients, three of whom had reported no previous depression at baseline or 6-day follow-up, and three of whom had been depressed only prior to CABG. Whilst depression has been associated with cognitive impairment, the two variables were not correlated and thus impairment is not explained by a depressed state.

The prediction of post-CABG impairment on the Stroop task was assessed further by multiple linear regression with the independent continuous variables of age, NART error score, and scores of extroversion and neuroticism. The regression showed the variables of age and NART to be significant predictors, together accounting for 34% of variance in Stroop performance at 6 days ($P<0.001$) and 24% at 6 months ($P<0.01$). Thus, patients who were older, and those of lower pre-morbid intellectual capacity, were more likely to suffer post-CABG deficit. The personality factors were not predictive.

Table 1 also shows mean Stroop performance at each time point as in a conventional analysis to describe impairment as a change from baseline. The performance profile shows an immediate post-operative deterioration in performance, which is then followed by a marked recovery at 6 months to a level substantially above that of the pre-operative baseline. The significant main effect of time (ANOVA: $F_{2,240}=8.70$, $P<0.001$) is located in significant differences between performance at 6 months and that at 6 days and baseline (Tukey post-hoc comparisons). The outcome of this mean-based analysis suggests an overall recovery of function at 6 months and is in contrast to the preceding analysis, based on assessment of absolute impairment, which shows some 40% of patients to be impaired at the second follow-up.

Discussion

The results confirm that pre-existing cognitive impairment is a significant determinant of whether deficits are observed after anaesthesia and surgery associated with CABG. Patients with a pre-existing attentional deficit as assessed by the Stroop task were significantly more likely to show post-CABG attentional impairment than those without such a deficit. MRI studies[21] indicate that CNS abnormalities resulting from the patients' chronic cardiac disease may underlie such pre-existing intellectual impairments.[22 23]

The results also fully replicate earlier findings[12–15] showing that post-CABG depression, too, is significantly determined by the patient's state prior to the procedure. More generally, the results support previous findings that CABG outcome is predicted by age and pre-morbid intellectual status.[16 24] Older patients, and those with lower pre-morbid intellectual function, were more likely to suffer post-CABG impairment.

Caution is required in extrapolating from the present study where only one cognitive assessment has been employed. Nonetheless, the obvious corollary of the results is that, unless allowance is made for pre-existing impairments, there is the risk of erroneously ascribing some adverse outcomes to a procedure and hence over-estimating its potential risks. Furthermore, where a procedure does exacerbate a pre-existing deficit, the full impact may be missed when using purely relative measures. For example, even a slight decline in the performance of an individual with a pre-existing impairment may be of considerable clinical consequence when compared with that of an individual without such impairment.

The latter issue of individual variation is also critical to full understanding of CABG-related impairment. It has been widely observed, both in the case of CABG and recovery from general anaesthesia, that individual variation is often masked when results are expressed in terms of group means and that this may lead to failure to detect both decline and improvement in a subgroup of patients.[2 22 25–27] The present analysis demonstrates that simply comparing average pre- and post-CABG performance does not accurately describe the adverse impact of CABG upon Stroop performance and the recovery of function. The mean-based analysis gives the impression of overall recovery of function at 6 months whereas the assessment of absolute impairment shows a substantial proportion of the patients still to be impaired.

Whilst the detection of impairment is a principal concern in studying outcome after CABG, it is important also to be aware of potential improvements in function because of the procedure. Eight of the present patients who were impaired prior to CABG improved significantly to unimpaired status 6 months after surgery. Their mean change in Stroop score of 18.5 (SD 9.47) corresponds to a 28% improvement from their baseline (t_7=4.55, P=0.003) and contrasts markedly with the 5% improvement due to practice typically seen in 'normal' subjects.[5] Whilst speculative given the present small sample, it has been proposed that such improvement reflects both practice and the beneficial effects of improved perfusion upon cognition.[23]

The present attrition rate of 32% is virtually identical to that of a very recent study of pre-existing depression and CABG[14] but it is higher than that of others.[12 13 15] Attrition commonly affects studies involving long-term follow-up and may result in fundamental differences between those who continue with a study and those who 'drop out'. Benedict[22] has observed that when a group of particularly impaired individuals drop out of a CABG data set there is then the potential for the procedure to appear to exert a less adverse effect. Further analysis of the present data confirms that, pre-operatively, the proportions of those impaired and depressed were considerably higher amongst the drop-outs than those who continued with the study (36 *vs* 16%, and 44 *vs* 28%, for impairment and depression, respectively). Whilst the differences are not statistically reliable because of the small numbers involved, they show that attrition has the potential to distort the results of such a study (P=0.21 and P=0.10, for impairment and depression, respectively). A similar effect of attrition is seen in the results of Vingerhoets and colleagues.[8] Some 48% of one of their CABG study groups dropped out between baseline and follow-up, the consequence being that the baseline Stroop performance of those who continued with the study (and against which long-term follow-up was evaluated) was some 23% better than that of the original sample.

Extensive studies of CABG-related cognitive deficits have led to detailed 'Consensus Statements' by Murkin and his colleagues regarding the tasks and methodology for such research.[4 25 28 29] The present results confirm the specific consensus regarding pre-operative assessment: 'A number of patients presenting [for CABG] may have pre-existing CNS abnormalities. [The] neuropsychologic state needs to be assessed[...] prior to operation to provide accurate baseline information.' (p. 1289).[25] The present results suggest that baseline information would be obtained more accurately with tasks that provide evidence of absolute functional status than the commonly used relative measures. They have the further virtue of being predictive of outcome.

The present results do not call into question the general principles outlined in the Consensus Statement for research into CABG impairment.[25] There would seem merit, however, in a series of studies to contrast absolute and relative measures of cognition in their ability both to detect pre-existing deficits and to predict subsequent CABG-related impairment. Indeed, retrospective analysis of some published data sets might be capable of addressing this question where those studies have involved tasks with absolute performance norms which were not employed in the original analysis.

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Fast-track cardiac anaesthesia in the elderly: effect of two different anaesthetic techniques on mental recovery[†]

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Elderly patients may be considered for 'fast-track' cardiac anaesthesia, but can suffer psychological complications and slow recovery of mental function after surgery, which can interfere with recovery. Reduced metabolism and changed distribution of anaesthetic and sedative agents can cause poor recovery. We made a prospective randomized comparison of mental function, haemodynamic stability and extubation and discharge times in elderly patients (65–79 yr) receiving two premedication, anaesthetic and sedative techniques. Patients received either propofol (n=39) (fentanyl 10–15 $\mu g\ kg^{-1}$ and propofol 2–6 $mg\ kg^{-1}$ intraoperatively and a propofol infusion for 3 h postoperatively) or premedication with lorazepam followed by midazolam for anaesthesia (n=39) (fentanyl 10–15 $\mu g\ kg^{-1}$ and midazolam 0.05–0.075 $mg\ kg^{-1}$ intraoperatively and a midazolam infusion for 3 h postoperatively). Impairment of mental function was noted in 41% of patients in the propofol group and 83% in the lorazepam and midazolam group (P=0.001) 18 h after extubation. Patients in the propofol group were extubated earlier [1.4 (SD 0.6) vs 1.9 (0.8) h, P=0.02]; and reached standard intensive care unit discharge criteria [7.6 (4.6) vs 14.2 (13) h, P=0.02] and hospital discharge criteria [4.3 (1.0) vs 4.9 (1.1) days, P=0.04) sooner than patients in the lorazepam and midazolam group, but actual discharge times did not differ between the groups. Haemodynamic values were stable in both groups.

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Fast-track cardiac anaesthesia aims to allow early tracheal extubation after cardiac surgery.[1] Prospective randomized controlled trials have shown the merits of this approach, which is now often standard for cardiac surgery.[1–4]

Coronary artery bypass (CABG) surgery is becoming frequent in the elderly (65–79 yr).[5] [6] Many institutions consider the elderly suitable for fast-tracking, but elderly patients are generally slower to recover and can develop delirium, confusion and agitation in the postoperative period, possibly caused by impaired drug distribution and metabolism. Poor mental performance after surgery reduces the ability of patients to communicate their needs and cooperate with medical staff, and may interfere with recovery.

We tested the hypothesis that anaesthesia and sedation with an agent with rapid clearance and less cumulative effects may cause less impairment of postoperative mental function and allow early extubation and recovery in elderly patients compared with a standard cardiac anaesthetic technique. We conducted a prospective randomized comparison of mental function, haemodynamic stability and extubation and discharge times in elderly patients, comparing propofol with midazolam for anaesthesia and sedation.

Methods

Patients and study groups

After Ethics Committee approval, 83 patients, aged 65–79 yr and undergoing elective CABG surgery, gave signed consent to participation in the study. Exclusion criteria

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included previous CABG or heart valve surgery; a left ventricular ejection fraction of <20%; documented myocardial infarction within the previous 6 weeks; overt congestive cardiac failure; inotropic therapy (excluding digoxin) or requirement for an intra-aortic balloon pump within 24 h of the study; a history of allergy to propofol or its constituents; severe chronic obstructive pulmonary disease requiring daily therapy with steroids or bronchodilators; renal insufficiency (creatinine concentration >150 mmol litre^{-1}); severe liver disease (alanine aminotransferase or aspartate aminotransferase >75 IU litre^{-1}); and a history of seizure or stroke. Patients who had a cardiopulmonary bypass time >120 min were also excluded.

Patients were randomized before surgery to either propofol or lorazepam and midazolam using a computer-generated randomization code. Medical and physical details were recorded.

Propofol group

Benzodiazepines were not used. Preoperative sedation consisted of morphine 0.15 mg kg^{-1} i.m. 1.5 h before surgery. Anaesthesia was induced with 10–15 μg kg^{-1} fentanyl with or without thiopental 50–75 mg i.v. Tracheal intubation was facilitated by pancuronium 0.15 mg kg^{-1}. Anaesthesia was maintained before cardiopulmonary bypass (CPB) with a propofol infusion at 2–6 mg kg^{-1} min^{-1} with or without 0.5–2% isoflurane. The propofol infusion was continued during CPB at 2–6 mg kg^{-1} h^{-1} and was reduced to 2 mg kg^{-1} h^{-1} before transfer to the intensive care unit (ICU). It was continued for 3 h in the ICU at 0.5–6 mg kg^{-1} h^{-1}. The propofol infusion rate was adjusted to give a Ramsay sedation score of between 3 (subject is drowsy but responds to commands) and 4 (subject is asleep but exhibits a brisk response to a light glabellar tap or a loud auditory stimulus)[10] (Appendix 1). Persistent hypertension (systolic blood pressure >140 mm Hg) was treated with nitroglycerine with or without nitroprusside infusion to achieve systolic arterial pressure of 90–130 mm Hg. Esmolol 20 mg or metoprolol 2–5 mg i.v. was used to control tachycardia (heart rate >110 beats min^{-1}). Hypotension (systolic arterial pressure <90 mm Hg) was treated with 500 ml of a colloid solution with or without dopamine infusion as dictated by the patient's haemodynamic values. Shivering was treated with pethidine 25–50 mg i.v. Indomethacin 50–100 mg was given in suppository form for analgesia when patients arrived in the ICU. Supplementary analgesia was with morphine boluses 1–4 mg h^{-1} i.v. after extubation.

Benzodiazepine group

Patients were given lorazepam 0.5–2 mg sublingually 1.5 h before surgery. Anaesthesia was induced with fentanyl 10–15 μg kg^{-1} with or without 50–75 mg thiopental i.v. Tracheal intubation was facilitated with pancuronium 0.15 mg kg^{-1}. Midazolam 0.05–0.075 mg kg^{-1} was given i.v. before CPB. Anaesthesia was maintained before and during CPB with 0.5–2% isoflurane and oxygen. After separation from CPB, a midazolam infusion at 0.01–0.05 mg kg^{-1} h^{-1} was started and maintained for 3 h in the ICU. The midazolam infusion rate in the ICU was adjusted to give a Ramsay sedation score of 3–4.[10] Treatment for shivering, pain and haemodynamic disturbances was the same as for the propofol group.

Surgical procedure

Surgery was standardized. Patients had a median sternotomy and internal mammary arteries and saphenous veins were taken for grafts. Myocardial protection was with intermittent antegrade cold blood cardioplegia given through the aortic root. Systemic temperature was allowed to drift to 33°C during CPB. Roller pumps and membrane oxygenators (Maxima Metronic, Minneapolis, MN) were used in all cases. Haematocrit concentrations were maintained between 20 and 25% and CPB flow rate between 2.0 and 2.5 litre min m^2. The mean perfusion pressure was kept at 50–60 mm Hg by titrating phenylephrine or nitroprusside. Patients were actively rewarmed to a nasopharyngeal temperature of 38°C before removal of the aortic cross-clamp and weaning from CPB.

After surgery

The infusions of propofol (propofol group) and midazolam (benzodiazepine group) were continued for 3 h in the ICU. Patients were ventilated artificially to maintain Pa_{CO_2} between 35 and 43 mm Hg and Pa_{O_2} >85 mm Hg. The sedative infusions were discontinued after 3 h if the patient achieved the following specific criteria:

(i) Cardiovascular stability (CI >2 litre m^2) with a dose of dopamine no more than 3 μg kg^{-1} min^{-1} or dobutamine no more than 5 μg kg^{-1} min^{-1}, and without using a mechanical assist device.

(ii) Minimal bleeding from chest drains (<50 ml h^{-1}).

(iii) Core body temperature >36.5°C.

(iv) Oxygen saturation of haemoglobin >95% with an inspired oxygen concentration of ≤60%.

(v) No electrocardiographic changes indicating new ischaemia or myocardial infarction.

Patients who did not meet the above criteria were excluded from the trial. Patients who met the above criteria were assessed every 15 min after stopping sedation to determine when they met prespecified extubation criteria.[1 3]

Outcome measurements

Mental function

The tests used were as follows:

Hopkins Verbal Learning Test (HVLT). This test was developed specifically for the elderly, and tests various aspects of learning and memory.[11] It requires accurate repetition of verbally presented word groups. The patient must recall as many words as possible from memory from a group of 12 words presented. We analysed three measures: (i) total recall—the total number of words recalled over three trials (maximum score is 36); (ii) delayed free recall (DFR)—the number of words recalled from the presented list after a 10 minute delay, (maximum score is 12); (iii) discriminability index (DI)—the number of words recognized from the presented list with category cues provided. The score is calculated by subtracting the number of false positives from true positives reported by the patient, and the maximum score is 12.

Trail-Making Test (Part A) (TMT-A).[12] Patients performed the TMT-A with their dominant hand free of i.v. or arterial catheters. This tests attention, concentration and visual tracking. It requires the simultaneous integration of several cognitive functions combined with a motor response. The test is scored by the number of seconds required to complete the trail.

Folstein Mini-Mental Scale Examination (MMSE).[13] This tests orientation, attention, calculation, instantaneous recall, short-term memory, language and visuomotor ability. The highest score is 30. It screens for cognitive impairment, with emphasis on orientation.

These tests were selected because they evaluated orientation, concentration, verbal learning and memory—functions that are important when assessing immediate or acute anaesthetic-related cognitive deficits. They were chosen considering the time available and the physical limitations of elderly patients after cardiac surgery.

Surgery started at 08:00 h. The psychological tests were timed to measure cognitive deficits caused by anaesthesia, as soon as possible after surgery. The MMSE was used 4 h after extubation to detect the earliest difference in cognitive recovery, particularly orientation, between the groups. All tests (total recall, DFR, DI, TMT-A, MMSE) were done 18 h after extubation (the morning after surgery) to allow comparison with baseline tests. Previous work[1] showed that patients receiving fast-track cardiac anaesthesia are discharged from intensive care at 31.6 (SD 14.3) h, so 18 h after extubation was a practical time to measure cognitive function.

A single examiner tested each patient before and after surgery, in a quiet environment free from distractions and interruptions. Testing took approximately 1 h. Because preoperative intelligence (IQ) is a potentially important confounder when measuring changes in cognitive function, IQ was tested using the National Adult Reading Test.[14] Anxiety can also confound measured changes in cognitive function. Anxiety was measured before surgery and 18 h after extubation using a State–Trait Anxiety Inventory Score.[15] Pain levels were measured with a visual analogue scale (VAS) hourly for 6 h and then 18 h after extubation, as pain can also affect cognitive tests. A clinical neurological examination evaluating power, tone, coordination and sensation was performed the morning after surgery in all patients. All patients were followed up by phone 6–12 months later to determine their functional status.

Mental impairment

A decline in mental function was calculated by considering the change in performance from the preoperative assessment to the 4- and 18-h assessments for each patient. Impairment was defined as a ⩾20% decline from the preoperative assessment to the postoperative assessment in one or more of the five tests (⩾20% of the tests performed).[16 17] In addition, the percentage of patients with a ⩾20% decline in each test from before to after operation was compared between the groups.

Extubation and discharge times

Extubation time was the time from stopping sedation to tracheal extubation. Standard discharge criteria[1 3] were used to assess when the patient was medically fit to be discharged from the ICU and hospital. The actual discharge time from the ICU was from entry to ICU to discharge from ICU and the actual discharge time from hospital was defined as the time from the day of surgery until discharge from hospital.

Level of consciousness

After extubation, the level of consciousness (LOC) and orientation were assessed at hourly intervals for 6 h using a 5-point LOC scale (Appendix 1) and a 10-point orientation scale (Appendix 2). A higher score on the LOC scale indicates a poorer LOC. After extubation, respiratory frequency was measured every 15 min for 1 h, then every 30 min for 1 h and hourly for the next 6 h. Arterial blood gases were measured before anaesthesia, 30 min before tracheal extubation and 30, 90 and 240 min after tracheal extubation.

Haemodynamic measurements

Heart rate, systemic blood pressure, pulmonary artery blood pressure, pulmonary capillary wedge pressure, central venous pressure and cardiac output were recorded at the following times: after induction, after intubation, after skin incision, after sternotomy, after CPB, after sternal closure, on arrival at the ICU, hourly in the ICU until the patient was extubated, then 10, 30 and 60 min after extubation and hourly for 4 h after extubation.

Postoperative complications

Perioperative myocardial infarction was diagnosed if either or both of the following findings were present: creatinine kinase isoenzyme MB (CK-MB) concentration greater than 50 IU litre^{-1} and representing more than 8% of the total creatinine kinase or electrocardiographic changes from baseline in two or more leads. Changes were defined as new Q waves of at least 0.04 s in duration and 1 mm in depth, ST-segment elevation or depression of >2 mm lasting 48 h, and a symmetrical T-wave inversion lasting >48 h. Blood was analysed for cardiac enzymes 8, 16 and 24 h after the release of the aortic cross-clamp. An electrocardiogram was done daily for 3 days after operation.

Reintubation, pneumothorax, cardiac or respiratory arrest, cardiac arrhythmias that required medical treatment, postoperative bleeding, reoperation, postoperative renal dysfunction (creatinine >150 μmol litre^{-1}), seizures and cerebrovascular accidents were recorded. Cerebrovascular accident was defined as a sudden onset of focal neurological deficit persisting >24 h, as documented by a neurologist. Intraoperative awareness with recall was assessed using a standard postoperative interview 18 h after extubation.[18] Mortality was defined as any death occurring during hospital stay.

Data collection and statistical analysis

Routine details were collected for each patient. All drugs (doses and infusion rates) given perioperatively were recorded. Patients who did not fulfil the necessary criteria to stop sedation were excluded from the trial and the reason for their failure was documented. These patients were excluded from the statistical analysis. Sample size calculation was done for an α error of 0.05, a β error of 0.8 and a proportion of 60% of patients with an episode of cognitive dysfunction in the benzodiazepine group reduced to 30% in the propofol group. Results are expressed as mean (SD) or median (range) as appropriate. Between-group analysis was with the unpaired *t*-test. Serial comparisons used either one-way analysis of variance or a two-way between-group analysis of variance with repeated measurements over time, followed by *post hoc* Tukey's test. Non-parametric data were analysed with the χ^2 test and the Mann–Whitney *U*-test. Logarithmic transformation of non-parametric data was performed where appropriate. Differences were considered significant if $P<0.05$. Statistical analysis was performed with SPSS for Windows version 6.1.2 on an IBM-compatible PC.

Results

Seventy-eight ($n=39$ for each group) of 83 patients enrolled completed the study. No patient was excluded because bypass time was greater then 120 min. Five patients were excluded after surgery because they did not reach the criteria for stopping sedation within the defined time. The reasons for failure in the benzodiazepine group included intraoperative anaphylaxis ($n=1$), reoperation for bleeding ($n=1$) and myocardial infarction ($n=1$); in the propofol group they included cerebrovascular accident ($n=1$) and high alveolar-to-arterial oxygen gradient ($n=1$). There were no systematic differences in baseline characteristics between the propofol and benzodiazepine groups (Table 1). The mean dose of lorazepam given to the patients in the midazolam group was 1.25 mg (range 0.5–2 mg). The two groups had an equal prevalence of medical problems preoperatively.

Cognitive impairment

There were no differences in baseline intelligence scores, state–trait anxiety scores or cognitive tests between the groups (Table 2). Eighty-three per cent of patients in the benzodiazepine group *vs* 41% of patients in the propofol group ($P=0.001$) had reduced scores 18 h after extubation, as defined by the 20% decline criterion (Fig. 1). The percentage of patients with a 20% or more decline in each test from baseline to 18 h after extubation is presented in Fig. 2. Fifty-five per cent of patients in the benzodiazepine group exhibited a 20% decline from baseline in the MMSE 4 h after extubation *vs* 22% of patients in the propofol group ($P=0.003$). Patients in the propofol group performed significantly better on the TMT-A ($P=0.007$) and DFR ($P=0.002$) 18 h after extubation than patients in the benzodiazepine group. Group scores (Table 2) of total recall, DFR and DI were significantly more reduced in the benzodiazepine group 18 h after extubation.

State anxiety scores were similar in both groups18 h after operation. Pain scores were low (mean VAS was 3.0 in the propofol group and 3.0 in the benzodiazepine group). No gross neurological deficit was detected in any patient the morning after surgery. At follow-up 6–12 months after surgery, all patients were functioning independently.

Table 1 Patient details. LVEF = left ventricular ejection fraction; CPB = cardiopulmonary bypass. Numbers in parentheses are SDs

	Propofol (*n*=39)	**Benzodiazepines** (*n*=39)
Age, yr	71.2 (3)	70.4 (3)
Sex, M/F	26/13	30/9
Weight, kg	78.3 (9)	77.6 (8)
Body surface area, m^2	1.78 (0.19)	1.89 (0.24)
Diabetes mellitus, %	32.5	30.6
Previous myocardial infarction, %	48	47.4
Hypertension, %	65	66
LVEF >60%/40–60%/20–40%, *n*	16/14/9	17/14/8
Aortic cross-clamp time, min	61.0 (16)	68.5 (16)
CPB time, min	81.0 (20)	89.1 (22)
CPB temperature, °C	33.7 (0.7)	33.8 (0.7)

Table 2 Cognitive scores. Data are mean (SD). MMSE = Mini-Mental State Examination; DI = discriminability index; DFR = delayed free recall; TMT-A = Trail-Making Test (Part A). *$P<0.05$

	Propofol (*n*=39)		**Benzodiazepines (*n*=39)**	
	Baseline	**18 h after extubation**	**Baseline**	**18 h after extubation**
MMSE, *n*	28.8 (1.3)	27.6 (2.1)	28.7 (1.3)	26.8 (2.8)
Total recall, *n*	19.8 (4.9)	16.9 (4.8)	19.1 (6.3)	16.3 (4.8)
DI, *n*	10.5 (1.7)	9.4 (2.0)	10.5 (3.6)	8.2 (3.0)*
DFR, *n*	8.1 (2.5)	6.2 (2.5)	7.9 (2.0)	4.2 (2.0)*
TMT-A, s	50.6 (15.2)	61.4 (25)	52.1 (18.4)	77.6 (26.5)*

Level of consciousness

The mean dose of midazolam administered in the ICU was 0.03 (range 0.01–0.045) mg kg^{-1} h^{-} and the mean dose of propofol was 1.8 (0.5–3) mg kg^{-1} h^{-1}. Use of postoperative opioids was similar in the two the groups. The total dose of prochlorperazine used was significantly greater in the propofol group. The propofol group had a significantly greater LOC score from the second hour after extubation (P=0.015) than the benzodiazepine group (Table 2). The propofol group also had significantly greater orientation scores for the first 4 h after extubation (P=0.005) than the benzodiazepine group (Table 3). Oxygen saturation, respiratory rate and arterial blood gases after extubation were similar in the two groups (Table 4).

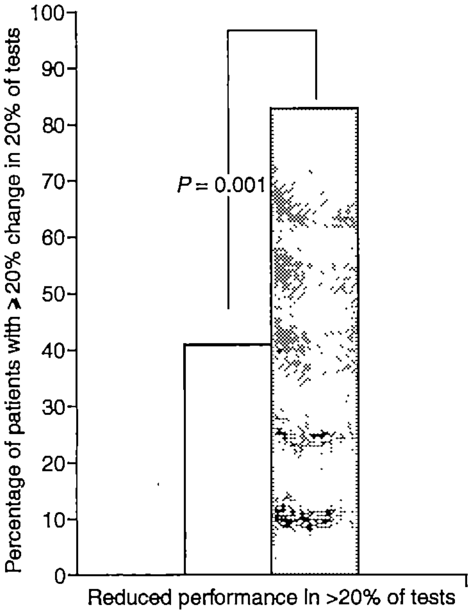

Fig 1 Reduced performance in 20% of tests 18 h after extubation. Open columns = propofol group; filled columns = benzodiazepine group.

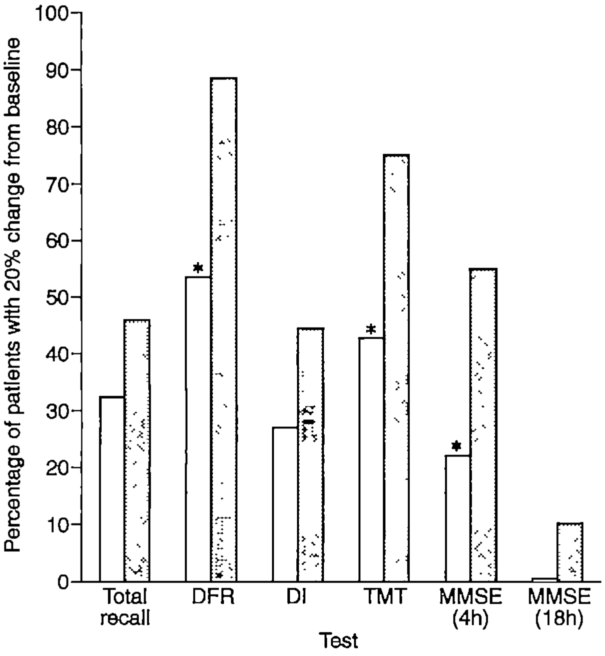

Fig 2 Reduction in mental function 18 h after extubation. Open columns = propofol group; filled columns = benzodiazepine group. DFR = delayed free recall; DI = discriminability index; TMT = Trail-Making Test (Part A); MMSE = Mini-Mental State Examination. *P<0.05

Haemodynamic measurements and cardiac morbidity

Haemodynamic values were stable throughout the study and similar in the two groups. Heart rate and mean arterial pressure (MAP) were significantly lower in the propofol group for the first 3 h in the ICU than in the benzodiazepine group (Table 5). There was no significant difference between the groups in intraoperative use of nitroglycerine (propofol group, n=22; benzodiazepine group, n=18), dopamine (propofol group, n=2; benzodiazepine group, n=2) or nitroprusside (propofol group, n=5; benzodiazepine group, n=3). In addition, there was no significant difference between the groups in the postoperative use of nitroglycerine (propofol group, n=2; benzodiazepine group, n=1) or dopamine (propofol group, n=0; benzodiazepine group, n=2). More patients received nitroprusside for hypertension in ICU in the benzodiazepine group (n=15) than in the propofol group (n=6) (P=0.02).

Extubation and discharge times

Extubation time (time from stopping sedation to extubation) was significantly less in the propofol group [median 1.5

Table 3 Level of consciousness scores. Data are mean (SD). *P<0.05

	LOC score		**Orientation score**	
Hours after extubation	**Propofol (n=39)**	**Benzodiazepines (n=39)**	**Propofol (n=39)**	**Benzodiazepines (n=39)**
1	1.63 (0.6)	2.5 (0.8)	9.03 (1.49)*	7.7 (2.5)
2	1.47 (0.5)*	1.91 (0.73)	9.59 (0.7)*	8.3 (2.1)
3	1.41 (0.5)*	1.75 (0.51)	9.56 (0.7)*	8.7 (1.4)
4	1.38 (0.4)*	1.78 (0.49)	9.69 (0.6)*	9.2 (1.2)
5	1.34 (0.48)*	1.72 (0.52)	9.6 (0.6)	9.4 (1.6)
6	1.34 (0.48)*	1.63 (0.49)	9.7 (0.68)	9.4 (1.2)

Table 4 Blood gas analysis 30 min after extubation. Data are mean (SD). RR = respiratory rate; Sa_{O_2} = arterial oxygen saturation; Pa_{O_2}/FI_{O_2} = Arterial partial pressure of oxygen/inspired oxygen fraction; Pa_{CO_2} = arterial partial pressure of carbon dioxide

	Propofol group	**Benzodiazepine group**
RR	14 (3)	13 (3)
Sa_{O_2}, %	96 (2)	96 (3)
Pa_{O_2}/FI_{O_2}	45 (8.3)	40 (7.5)
Pa_{CO_2}, mm Hg	44.2 (9)	47.3 (9)

Table 5 Perioperative haemodynamic measurements. Data are mean (SD). OT = operating theatre; CPB = cardiopulmonary bypass; ICU = intensive care unit. *P<0.05

	Heart rate (beats min–1)		**Mean arterial pressure (mm Hg)**	
	Propofol (*n*=39)	**Benzodiazepines (*n*=39)**	**Propofol (*n*=39)**	**Benzodiazepines (*n*=39)**
Arrival in OT	62 (12)	64 (11)	102 (19)	100 (14)
After sternotomy	63 (12)	66 (12)	95 (18)	91 (18)
After CPB	79 (10)	83 (9)	76 (10)	76 (11)
Arrival in ICU	76 (12)	80 (12)	71 (12)	76 (12)
1st hour in ICU	76 (9)*	82 (10)	74 (8)*	80 (10)
2nd hour in ICU	77 (9)*	84 (10)	76 (9)*	80 (9)
3rd hour in ICU	78 (9)*	83 (11)	77 (9)	75 (10)
Extubation	84 (10)	83 (12)	85 (12)	85 (11)
1 h after extubation	84 (12)	88 (11)	80 (10)	80 (12)
4 h after extubation	83 (12)	88 (11)	79 (8)	77 (9)

Table 6 Extubation and discharge times. Data are median (range). ICU = intensive care unit. *P<0.05

	Propofol	**Benzodiazepines**
Extubation time, h	1.5 (0.4–7.1)*	1.8 (1–8.9)
ICU		
Discharge criteria met, h	6.1 (4 –109)*	9.25 (4.2–70.7)
Actual discharge time, h	24 (15.1–120)	26 (20–74.6)
Hospital		
Discharge criteria met, days	4.0 (3–11)*	5.0 (3–16)
Actual discharge time, days	6.0 (4–21)	6.0 (4–17)

Table 7 Complications. MI = myocardial infarction; LCO = low cardiac output; CVA = cerebrovascular accident; GI = gastrointestinal. †18 atrial arrythmias, 1 ventricular arrhythmia; ‡15 atrial arrhythmias, 3 ventricular arrhythmias

Complication (*n*)	**Propofol (*n*=39)**	**Benzodiazepines (*n*=39)**
Myocardial infarction, *n*	0	0
Low cardiac output syndrome, *n*	1	1
Cerebrovascular accident, *n*	0	0
Reintubation, *n*	1	0
Bleeding from chest drains, *n*	5	2
Arrhythmia, *n*	19†	18‡
Renal insufficiency, *n*	3	3
Gastrointestinal bleeding, *n*	1	0
Pneumothorax, *n*	1	0
Death, *n*	0	0

(range 0.4–7.1) h] compared with the benzodiazepine group [1.9 (1–7.9) h] (P=0.02). Patients in the propofol group reached ICU discharge criteria significantly earlier [6.1 (4–109) h] than patients in the benzodiazepine group [9.2 (4.2–70.7) h] (P=0.04), and reached hospital discharge criteria significantly earlier [4 (3–11) days] than patients in the benzodiazepine group [6 (4–17) days]. Actual ICU or hospital length of stay did not differ between the groups (Table 6).

Postoperative complications

The incidence of postoperative treated complications was similar in the two groups (Table 7). No patient suffered a myocardial infarction, cerebrovascular accident or death.

Discussion

We found that elderly CABG patients receiving a low-dose narcotic and propofol regimen have less mental impairment immediately after surgery, are extubated earlier and reach the criteria for ICU and hospital discharge earlier than elderly patients receiving low-dose narcotic and benzodiazepine premedication, anaesthesia and sedation.

More elderly patients are now undergoing CABG surgery.[5 6] Older patients are extubated less quickly after cardiac surgery,[19] but there was no difference in 30-day mortality or postoperative complications in elderly [mean age 75 (4) yr] compared with young [mean age 56 (14) yr] patients undergoing early extubation (4–8 h) after CABG surgery.[20] A retrospective review of fast-track cardiac surgery in elderly patients [mean age 62.4 (9.4) yr] found decreased LOS and no greater postoperative morbidity or mortality compared with a previous conventionally treated group.[21] The present study supports the contention that all patients, including the elderly, should be considered for early extubation.[22]

For early tracheal extubation after cardiac surgery, patients must recover from the anaesthetic and sedative drugs used perioperatively. Elderly patients have reduced renal clearance and reduced hepatic metabolism of drugs.[23–25] In addition, the percentage of body weight composed of adipose tissue increases with age, thereby increasing the volume of distribution and the elimination half-life of lipid-soluble drugs.[23 26]

Ageing increases the pharmacodynamic sensitivity to the hypnotic effects of benzodiazepines[9 27] and is associated with decreased clearance of benzodiazepines.[28 29] This increased sensitivity and prolonged clearance results in slower recovery after anaesthesia and sedation with benzodiazepines. These altered effects of benzodiazepines in the elderly may explain the longer time to extubation in the benzodiazepine compared to the propofol group found in this study.

A recent study by Butterworth *et al.* concluded that short-acting drugs (opioid and neuromuscular blockers) have no association with length of stay in the ICU after extubation, or length of stay in hospital after CABG surgery [mean age 63 (11) yr].[30] However, the study did not examine the use of benzodiazepines or propofol in relation to length of stay, and was limited by a retrospective multicentre design and lack of standardized extubation or discharge criteria among centres. Barrientos-Vega *et al.* found that propofol resulted in a shorter extubation time than midazolam in general intensive care patients.[31] The pharmacokinetic profile of propofol[32–35] favours earlier recovery from anaesthesia and sedation and thus earlier extubation.

Anaesthesia and surgery affect mental function in the elderly and the risk increases with age. This effect appears to be independent of hypoxaemia and hypotension in non-cardiac surgery, suggesting an effect of anaesthetic agents on central neurotransmission. The propofol group had significantly less impaired LOC scores and orientation scores from the second hour after extubation than the benzodiazepine group. We believe that it is important to have patients conscious and orientated early after surgery. A conscious and orientated patient will communicate their needs and cooperate with the medical staff providing postoperative care. The ability to concentrate and learn instructions may facilitate tracheal extubation, chest tube removal and cooperation with physiotherapists and nursing staff.

Benzodiazepines cause antegrade amnesia and impairment of cognitive and psychomotor functioning,[36] which may explain the poorer early recovery in the immediate postoperative period in the benzodiazepine group seen in this study.

Extubation and discharge times

Patients in the propofol group met discharge criteria from the ICU and hospital significantly earlier than patients in the benzodiazepine group. However, there was no difference in actual discharge times from the ICU or hospital. There is a general reluctance to transfer patients out of the ICU during the night because of risks of complications and the inconvenience of shifting bed assignments. Standard discharge criteria provide an objective end-point in medical fitness for discharging patients from ICU or for reducing the intensity of nursing care.

Haemodynamic effects

There were no significant differences in intraoperative haemodynamics between the two groups. Patients in the propofol group had a significantly lower heart rate and MAP for the first 2 h after arrival in the ICU than patients receiving benzodiazepines, but these haemodynamic effects did not require intervention. Moderate slowing of heart rate has previously been associated with propofol infusion.[37]

Economics

This study did not analyse the cost-effectiveness of the fast-track anaesthetic regimens used. Although the effectivenesses of benzodiazepines and propofol for patient sedation are comparable, it is difficult to compare individual doses of these two agents. To overcome this problem a routine sedation score (Ramsay score) was used to guide infusion rates after surgery in this study, as recommended by other authors.[38] Propofol is two to three times as expensive as midazolam. However, some authors have argued that propofol is associated with more rapid awakening and therefore may give a shorter weaning time, which affects the final cost.[31 39]

Acknowledgements

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Appendix 1

Ramsay sedation score

1 = Patient anxious and agitated or restless or both.
2 = Patient cooperative, orientated and tranquil.
3 = Patient responds to commands only.
4 = Patient shows a brisk response to a light glabellar tap or loud auditory stimulus.
5 = Patient shows a sluggish response to a light glabellar tap or loud auditory stimulus.
6 = Patient shows no response to a light glabellar tap or loud auditory stimulus.

Appendix 2

Level of consciousness score

1 = Alert. Awake, meaningful, interpersonal interaction is occurring.
2 = Lethargic. Tends to drift off to sleep when not stimulated. Spontaneous movements are decreased and awareness is limited.
3 = Obtunded. Difficult to arouse; when aroused is confused. Constant stimulation is required to elicit even marginal cooperation from the patient.
4 = Stuporous. Does not rouse spontaneously; when aroused only groans, mumbles and moves restlessly in bed.
5 = Comatose. Completely unarousable; no evidence of behavioural response to stimulation.

Appendix 3

Orientation score

What year is it now?
What month is it now?
What is the date of this month?
What day of the week is this?

What season is this?
What country are we in?
What province are we in?
What city are we in?
What hospital are we in?
What floor of the hospital are we currently on?
Orientation is calculated by giving 1 point for each correct response
Total score: _/10.

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Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy

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In the present double-blind study we aimed to evaluate the postoperative analgesic effects of intrathecal midazolam with bupivacaine following haemorrhoidectomy. Forty-five patients were randomly allocated to one of three groups: the control group received 1 ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline intrathecally, group BM1 received 1 ml of 0.5% bupivacaine plus 0.2 ml of 0.5% preservative-free midazolam and group BM2 received 1 ml of 0.5% bupivacaine plus 0.4 ml of 0.5% midazolam. Time to first analgesia was significantly greater in the midazolam groups than in the placebo and significantly less in the BM1 group than in the BM2 group.

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Since the early 1980s, intrathecal administration of midazolam has been reported to have antinociceptive action[1] and to be an effective analgesic agent in animals[2 3] and humans.[4–7]

After haemorrhoidectomy, many patients require parenteral oral opioids and/or nonsteroidal antiinflammatory drugs (NSAIDs) for analgesia. The use of opioids in intrathecal or epidural anaesthesia has become popular to optimize postoperative analgesia. However, opioid-induced side effects, such as respiratory depression, nausea, vomiting, urinary retention and pruritus, limit their use.[8 9] The purpose of our study was to assess the effects of intrathecal midazolam as an adjunct to intrathecal bupivacaine after haemorrhoidectomy.

Methods

After local ethics committee and written informed consent had been obtained, 45 patients (ASA I–II) scheduled to undergo elective haemorrhoidectomy were enrolled in this double-blind, randomized trial. Those who had a contra-indication to regional anaesthesia or were opioid-tolerant were excluded. No premedication was given. The control group received intrathecally 1 ml of 0.5% heavy bupivacaine plus 0.2 ml of 0.9% saline; group BM1 received intrathecally 1 ml of 0.5% bupivacaine plus 1 mg of midazolam in 0.2 ml (5 mg ml^{-1}); and group BM2 received intrathecally 1 ml of 0.5% bupivacaine plus 2 mg of midazolam in 0.4 ml (5 mg ml^{-1}). Midazolam (Domicum; Hoffman-La Roche, Basle, Switzerland) available in our hospital contains midazolam hydrochloride buffered to pH 3.5 with sodium hydroxide and hydrochloric acid with no preservative.

Saddle block anesthesia was performed in the sitting position under aseptic conditions using a 25 G spinal needle and the subarachnoid space was entered at the L3–4 level. Patients were kept in the sitting position for 5 min, tested for sensory loss and then placed in the prone position before surgery.

During surgery, patients were monitored with electrocardiography, pulse oximetry and non-invasive measurement of arterial pressure and heart rate. After surgery, all patients were admitted for 1 day and instructed to take two Codety tablets (each tablet containing 300 mg paracetamol and 30 mg codeine phosphate) every 4 h as needed. No other analgesic was allowed during the 24 h after surgery.

Three parameters were assessed in this study: duration of effective analgesic time from the spinal anaesthesia; visual analogue scales (VAS) at first analgesia; and total consumption of analgesics in the 24 h after spinal anaesthesia. Any adverse events were also recorded. Neurological changes, such as motor and sensory deficits, bowel and

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Table 1 Patient characteristics and duration of surgery (mean (SD) or number). The control group received 1 ml of 0.5% bupivacaine and 0.2 ml of 0.9% saline; the BM1 group received 1 ml of 0.5% bupivacaine and 1 mg of midazolam in 0.2 ml; and the BM2 groups received 1 ml of 0.5% bupivacaine and 2 mg of midazolam in 0. 4 ml; none of the differences were significant

	Control group	BM1 group	BM2 group
Gender (male/female)	6/9	6/9	5/10
Age (yr)	44.2 (10.9)	41.5 (9.7)	43.7 (13.5)
Height (cm)	164.2 (9.1)	161.8 (8.5)	163.7 (9.3)
Weight (kg)	65.7 (11.6)	60.4 (10.4)	64.0 (10.5)
Duration of surgery (min)	26.3 (6.7)	28.0 (6.2)	26.4 (6.0)

Table 2 Postoperative analgesia. Values are mean (SD). *$P<0.01$ compared with the control group, †$P<0.05$ compared with the BM1 group

	Control group	BM1 group	BM2 group
Time to first pain medication (h)	3.99 (0.78)	6.03 (1.49)*	8.37 (2.51)*†
VAS at first pain medication (mm)	35 (9.2)	36 (9.1)	34 (9.9)
Number of oral administrations of Codety requested in 24 h	3.73 (0.79)	2.53 (0.74)*	1.80 (0.94)*

bladder dysfunction, were checked before discharge. The anaesthetist who performed subarachnoid block was not involved in assessment of patients and the observers were blinded.

Data are expressed as mean (SD). Statistical analysis was performed using the computer program SPSS (version 9.0; SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used for normally distributed parametric data. Time to first analgesia, pain scores at first pain medication and the number of analgesics requested in 24 h were analysed by the Kruskal–Wallis test followed by the *post hoc* multiple comparison test using the Dunnett method. $P<0.05$ was considered statistically significant.

Results

There were no significant differences between the groups in patient characteristics or duration of surgery (Table 1).

Time to first analgesia in groups BM1 and BM2 was significantly longer than that in the control group ($P<0.01$ in both cases). Time to first analgesia in group BM1 was also significantly less than that in group BM2 ($P<0.05$) (Table 2). There were no significant differences in VAS on analgesia administration among the three groups (Table 2).

All patients required analgesia during the 24 h after surgery. The number of oral administrations requested in this period was significantly less in the BM1 and BM2 groups than in the control group ($P<0.01$ in each case). There was no significant difference in frequency of analgesic rescue between the BM1 and BM2 groups ($P=0.073$) (Table 2).

There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients. Three of the 15 patients from each group developed urinary retention. Time to the first episode of self-voiding was similar in all groups. No neurological deficits were detected at discharge (Table 3).

Table 3 Postoperative side effects; values are mean (SD) or number of patients

	Control group	BM1 group	BM2 group
Nausea/vomiting	1	0	0
Sedation	0	0	0
Urinary retention	3	3	3
Time to first self-voiding (h)	4.99 (2.99)	4.95 (2.56)	5.31 (2.12)

Discussion

In this study, we found that the analgesic effect of intrathecal bupivacaine was potentiated by intrathecal midazolam. The addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by approximately 2 h and 4.5 h, respectively, compared with controls after haemorrhoidectomy. In addition, midazolam-treated groups used less analgesic in the first 24 h after surgery. Our results suggest a dose-dependent effect of intrathecal midazolam.

This study may be criticized on account of the different volumes of subarachnoid injection (1.2 ml was injected in the control and BM1 groups; and 1.4 ml in the BM2 group) and the consequent differences in bupivacaine concentration. However, Van Zundert and colleagues[10] have shown that the concentration and volume do not affect sensory block, motor block or duration of spinal anesthesia as long as the dose of local anaesthetic is constant.

In vitro autoradiography has shown that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation.[11] In 1987, Goodchild and Serrao reported that benzodiazepines might have analgesic effects at the spinal cord level in animals.[2] Analgesic efficacy of intrathecal midazolam in humans has been demonstrated recently.[5–7] The δ-selective opioid antagonist, naltrindole, suppresses the antinociceptive effect of intrathecal midazolam,[12] suggesting that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal δ receptors.

The most serious risk of intrathecal midazolam is its possible neurotoxicity. So far, animal studies have revealed no damage to the spinal cord, nerve roots or meninges.[13] There have been some reports on the spinal application of midazolam in humans. A single intrathecal injection of 2 mg midazolam did not cause any clinical neurological deficits and produced significant analgesia for 2 months in patients with chronic low back pain.[5] Intrathecal midazolam was also effective after leg surgery, without any side effects.[4] In addition to the effectiveness of intrathecal midazolam against somatic pain, an antinociceptive effect against visceral pain has been demonstrated in rabbits subjected to intestinal distension[3] and in humans after caesarean section.[6] Intrathecal midazolam has been used in a continuous infusion with doses of ≤6 mg day^{-1} for a long-term period in four patients with refractory neurogenic and musculoskeletal pain.[7] *In vitro* studies have suggested that clinically useful doses of intrathecal midazolam are unlikely to be neurotoxic.[14] In our study, we paid special attention to any potential side effects or complications during the perioperative period. There were no neurological complications. The analgesic effect of intrathecal midazolam was segmental, with no alteration in sympathetic tone or reflexes.

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Comparison of two neurostimulation techniques for axillary brachial plexus blockade

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This prospective, randomized, double-blind study compared two techniques of axillary brachial plexus block using a peripheral nerve stimulator. Both groups received initial musculocutaneous nerve block followed by either a single injection on median nerve stimulation (group 1) or a double injection divided between median and radial nerves (group 2). All 60 patients received a total of 30 ml of lidocaine 15 mg/ml with epinephrine 5 μg/ml. Complete sensory blockade of all six peripheral nerves occurred in 53% and 97% of patients in groups 1 and 2, respectively ($P<0.001$), with a more rapid onset of blockade occurring in group 2 patients ($P<0.001$). Complete motor blockade was evident in 30% and 83% of patients in groups 1 and 2, respectively ($P<0.001$).

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Keywords: brachial plexus, axillary approach; technique, nerve stimulation

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The many approaches used for brachial plexus block are well described. The choice usually involves personal preference based on the perceived efficacy of block in the surgical territory involved balanced against specific adverse effects in individual patients. The axillary approach avoids the more significant adverse effects of the more proximal approaches but suffers from inconsistency in achieving complete blockade. Recent improvements have centred around the use of the peripheral nerve stimulator to localize nerves accurately, while avoiding deliberate arterial puncture or the eliciting of paraesthesia.

The purpose of this study was to examine the extent of local anaesthetic blockade within all the nerves of the plexus using two different nerve stimulator techniques by the axillary approach.

Patients and methods

The study received approval from the Tayside Medical Ethics Committee. Sixty patients, ASA 1–3, aged ⩾17 yr, presenting for elective upper limb surgery were randomly allocated to receive one of two techniques for axillary brachial plexus block. Patients refusing a local anaesthetic technique were excluded, as were those with dementia, peripheral neuropathy or sensitivity to amide local anaesthetics.

All patients were visited before surgery and were given a full explanation; informed consent was obtained. On a patient's arrival in the anaesthetic room, a 20G intravenous cannula was inserted in the hand not being operated upon and full non-invasive monitoring commenced (NIBP, ECG, Sp_{O_2}). A small dose of midazolam (1–2 mg) was administered and oxygen 2 litres min^{-1} was delivered through a nasal cannula. With the patient lying supine, with their head placed on a pillow, the arm was abducted to 90° and the axillary artery palpated. The skin was cleaned and then anaesthetized with 1–2 ml of plain lidocaine 10 mg ml^{-1}. Neural blockade was facilitated using a 22G insulated short-bevelled needle and peripheral nerve stimulator (Stimuplex; B. Braun Medical). All patients received a total of 30 ml of lidocaine 15 mg ml^{-1} with epinephrine 5 μg ml^{-1}.

With both techniques, the musculocutaneous nerve was first located by eliciting maximal biceps contraction with a current of 0.5 mA and 5 ml of the local anaesthetic solution was injected. Then, from the same injection site in the distal axilla, 15–20 mm distal to the pectoralis major tendon, further injections were carried as follows (Figure 1). In group 1 (single-injection technique), the median nerve was located by eliciting the maximal flexor response in the fingers of the hand with a current of 0.5 mA and a total of 25 ml of lidocaine 15 mg ml^{-1} with epinephrine was then injected. In group 2 (double-injection technique), the median nerve was located as above and 15 ml lidocaine 15 mg ml^{-1} with epinephrine was injected. The radial nerve was then located by eliciting the maximal extensor response in the fingers and wrist with a current of 0.5 mA. A further

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10 ml of lidocaine 15 mg ml^{-1} with epinephrine was then injected.

Cutaneous analgesia was assessed 10, 20 and 30 min after completion of injection by an independent and blinded observer. Using a short-bevelled 27G needle, all six upper limb areas—median, musculocutaneous, ulnar, radial and medial cutaneous nerve of arm and forearm—were tested for complete sensory loss. Inability to move the relevant muscle groups of the limb against gravity was taken as the motor block end-point. Analgesic failure was managed with peripheral local anaesthetic supplementation or general anaesthetic as appropriate. Intraoperative sedation was provided by an intermittent bolus of midazolam if requested.

Duration of surgery, tourniquet discomfort or any additional problems, such as vascular puncture, were noted. All brachial plexus blocks were carried out by one operator (D.C.) and assessed by one blinded assessor (M.T.). Assuming a success rate of 60% with one technique against 90% for the second, 29 patients in each group would be required to show a significant difference at 80% power. Statistical comparisons were made using the Fischer exact test.

Results

There were no differences in patient characteristics between groups, nor any differences in type or duration of surgery (Table 1). It was possible to locate the desired nerves in all patients of both study groups. Sensorineural blockade of all six nerves occurred in 16 patients in group 1 (53%) and 29 patients in group 2 (97%) (P<0.001) (Table 2). The radial nerve was consistently blocked in all cases in group 2 but in only 18 patients (60%) in group 1 (P<0.001) (Table 3). Only one patient in group 1 had complete nerve blockade at 10 min compared with 14 patients in group 2 (P<0.001), and at 20 min, 27 patients (90%) in group 2 had complete sensory loss compared with seven (23%) in group 1 (P<0.001). Motor blockade was significantly better in group 2 than group 1 (P<0.001), with the radial being the nerve most

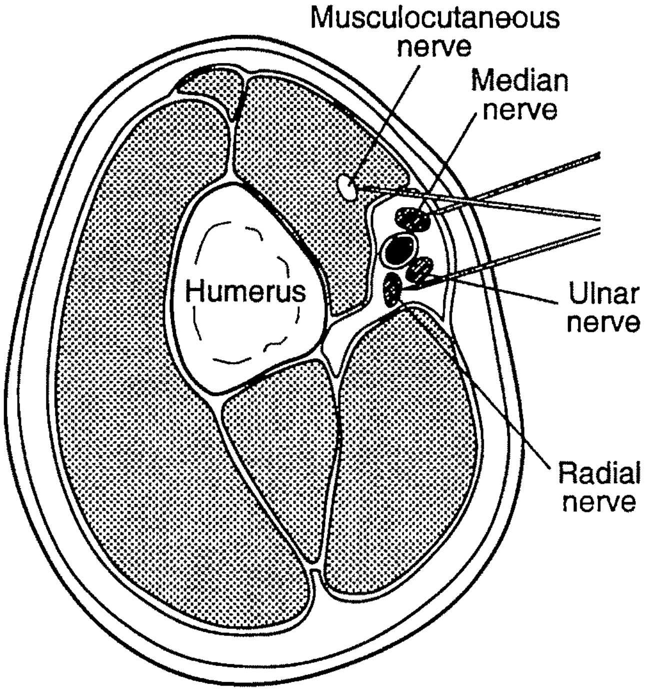

Fig 1 Transverse section through the proximal humerus showing the relationship of the brachial plexus nerves to the axillary artery.

Table 1 Patient characteristics

	Group 1 (n=30)	Group 2 (n=30)
Gender (M/F)	14/16	13/17
Age, yr (median (range))	52 (20–85)	55 (23–84)
Weight, kg (median (range))	69 (52–95)	66 (48–98)
Duration, min	33 (10–110)	42 (10–190)
Operations performed		
Dupuytren's	7	5
Carpal tunnel	9	8
Tendon surgery	5	4
Arthrodesis/arthroplasty	3	5
Wrist arthroscopy	1	2
Miscellaneous	5	6

Table 2 Pattern of sensory blockade. *P<0.001

Complete block at	Group 1 (n=30)	Group 2 (n=30)
10 min	1	14*
20 min	7	27*
30 min	16	29*

Table 3 Effectiveness of brachial plexus blockade. *P<0.001

Nerve blocked	Group 1 (n=30)	Group 2 (n=30)
Musculocutaneous	30	29
Median	29	30
Medial cutaneous of arm	29	30
Medial cutaneous of forearm	30	30
Ulnar	29	30
Radial	18	30*
Supplemented	3	0

Table 4 Pattern of motor blockade. *P<0.001

	Group 1 (n=30)	Group 2 (n=30)
Complete motor block	9	25*
Incomplete musculocutaneous	1	1
Incomplete median	3	2
Incomplete ulnar	4	3
Incomplete radial	17	2*

difficult to block completely by the single-injection technique (Table 4). No patient required general anaesthesia, but three patients in group 1 required supplemental nerve blocks.

Discussion

The axillary approach to brachial plexus anaesthesia is popular because of its ease of performance, clear vascular landmark and low incidence of complications.[1] Many of the traditional approaches have, however, suffered from inconsistency in blocking the musculocutaneous and radial nerves in particular.[2] Different agents and volumes of local anaesthetic, as well as a variety of methods for placing the local anaesthetic, have been described in an attempt to improve efficacy. These include feeling for 'fascial pops', trans-arterial methods and use of nerve stimulators.[3]

The trans-arterial approach appears to be both unnecessary and undesirable. Axillary block complicated by haematoma and nerve injury[4] or by false aneurysm formation[5] has been reported using this method and, as our study demonstrates; other methods avoiding this risk can be very effective. Another issue is whether large-volume single injections are as reliable as multiple-injection techniques. The failure rate remains significant for the 'single-shot, high volume' techniques often described in textbooks,[6] even when specific blocking of the musculocutaneous nerve is included, and this is reinforced by the findings in our single-injection patients, even when performed with a peripheral nerve stimulator.

CT studies by Thompson and Rorie[7] attributed this failure to anatomical variability in the septae within the neurovascular sheath creating a multi-compartmental structure which limits circumferential spread; they advocated the use of a multiple-injection approach. Vester-Anderson and colleagues[8] showed, using a catheter technique, that even volumes of ≤80 ml of local anaesthetic cannot reliably block the musculocutaneous nerve, which is essential for complete sensory analgesia of the limb and to prevent tourniquet discomfort and unwanted arm movement during surgery.

Some investigators have shown a favourable success rate with single-shot techniques with an end-point of 'readiness for surgery', but in these studies there may have been a predominance of palmar surgery. Lavoie and colleagues[9] compared single and multiple injections using a nerve stimulator and demonstrated the benefit of considering the musculocutaneous nerve as a separate, preliminary part of any axillary brachial plexus block. However, despite correctly determining the sensory block of each nerve ≤30 min after injection, they failed to detail those findings, confining themselves to recording adequacy for surgery as the study end point, rather than completeness of brachial plexus anaesthesia. Only 48% of the surgery in this study was restricted to the palmar surfaces of the hand, leaving radial nerve blockade desirable in 34% and essential in 18%.

The use of the peripheral nerve stimulator for brachial plexus block can improve success rates for both the regular practitioner of regional anaesthesia[10] and the occasional user,[11] combined with a reduced theoretical risk of nerve damage.[12] We designed our study to start with the identification and blocking of the musculocutaneous nerve in both groups, as that nerve lies within the body of coracobrachialis muscle at the distal axillary level and is outwith the connective tissue sheath. Thereafter, we compared a single 'intra-sheath' injection (by identifying the median nerve), with a more specific localization of the median and radial nerves. The order in which each nerve is localized and blocked is important to minimize the theoretical risk of nerve injury. In this we disagree with Gaertner and colleagues,[13] who suggested a sequence of nerve blockade as follows: median, ulnar, radial, musculocutaneous and medial (brachial and antebrachial) cutaneous nerves. This implies that whilst seeking the musculocutaneous nerve, the area of the median nerve may be recrossed some time after it has had local anaesthetic applied and risks transfixion of that nerve. In our study, the musculocutaneous nerve, outside the sheath, above and posterior to the artery, was blocked first. The needle was then withdrawn to and directed towards the artery to find the median nerve, and finally the needle was directed inferior to the artery to define the radial nerve (Figure 1). Following this sequence removes the risk of transfixing a nerve already partially blocked by a previous injection. Our experience with this double-injection technique is that there is little interference with localization of each nerve, even with the use of the more rapid onset local anaesthetic agents such as lidocaine.

This study revealed that the double-injection technique can have significant advantages over the single-injection technique in both speed of onset and pattern of block. Ninety per cent of blocks in the double-injection group and 23% in the single-injection group were deemed complete at 20 min. The pattern of sensory block showed the radial nerve to be incompletely blocked in 40% of patients having the single-injection technique, even after 30 min, compared with none in the double-injection group. It is also interesting to note that the ulnar nerve was blocked in 100% of the double-injection group despite no attempt to localize it. Motor blockade testing also showed significant advantage in the double-injection technique, 83% having complete motor blockade compared with 30% in the single-injection group. The double-injection technique in which the radial nerve is specifically identified has a faster onset and more complete sensory block.

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Dexamethasone is a cost-effective alternative to ondansetron in preventing PONV after paediatric strabismus repair

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This study evaluated the antiemetic efficacy, cost-effectiveness and clinical utility of prophylactic ondansetron and dexamethasone compared with placebo in the prevention of postoperative nausea and vomiting (PONV) in 135 children (2–15 yr, ASA I–II) undergoing strabismus repair. After induction with halothane and nitrous oxide in oxygen or i.v. thiopental, the children received i.v. dexamethasone 1 mg kg^{-1} to a maximum of 25 mg, ondansetron 100 μg kg^{-1} to a maximum of 4 mg or placebo (n=45). Episodes of PONV were recorded for the first 24 h after the operation. True outcome measures (parental satisfaction score, duration of stay in the postanaesthesia care unit and fast tracking time), therapeutic outcome measures (number needed to prevent (NNTP) PONV) and the cost to benefit a child with each drug were analysed. The incidence and severity of PONV in the first 24 h were significantly less in the dexamethasone and ondansetron groups than in the placebo group (P<0.05). The incidence (P=0.04) and severity (P=0.03) of PONV at the 6–24 h epoch were significantly less in the dexamethasone group than in the ondansetron group. Recovery time (P=0.07), fast tracking time (P=0.6), parental satisfaction scores (P=0.08) and NNTP PONV were comparable (NNTP=2) in both the ondansetron and the dexamethasone group. The cost to benefit a child with dexamethasone was approximately 22 times less than that of ondansetron.

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Postoperative nausea and vomiting (PONV) remains a distressing and common problem after strabismus repair despite the use of currently available antiemetics. Ondansetron is commonly used because of its efficacy and safety compared with other antiemetics, but its use has been criticized because of cost. A meta-analysis that reviewed the efficacy and safety data for ondansetron for preventing PONV has challenged the practice of routine prophylactic ondansetron based on benefit and risk.[1] Moreover, a number of studies and meta-analyses which evaluated the effects of ondansetron on PONV have reported surrogate outcome measures, such as the incidence of PONV and the number of emetic episodes per patient, rather than more meaningful outcome measures, such as patient satisfaction, hospital stay and the incidence of unanticipated hospital admission.[2] The higher cost of ondansetron has been a significant factor limiting its routine prophylactic use. Dexamethasone 1 mg kg^{-1} (maximum 25 mg) has been shown to be an effective prophylactic antiemetic for PONV in children undergoing ambulatory adenotonsillectomy.[3] In our study, we aimed to compare the efficacy, safety, cost-effectiveness and clinical utility of prophylactic dexamethasone, ondansetron and placebo with clinically more useful non-surrogate, therapeutic and pharmacoeconomic outcome measures.

Materials and methods

After obtaining institutional review board approval and informed parental consent, in this prospective, randomized, placebo-controlled, double-blinded study we enrolled 135 ASA physical status I or II children between the ages of 2 and 15 yr who were undergoing strabismus repair under general anaesthesia. We excluded children who had

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received drugs with antiemetic effects (e.g. phenothiazines, benzamides, scopolamine, corticosteroids and tricyclic antidepressants) in the 24 h before surgery. Children did not consume milk or solid food for at least 6 h before operation; clear fluids were allowed until 3 h before induction. We did not control the volume of fluid children ingested within 3 h before surgery.

Children were not premedicated. Anaesthesia was induced with halothane and nitrous oxide in oxygen via a facemask or with i.v. thiopental. After induction of anaesthesia and establishment of venous access, tracheal intubation was facilitated with 100 $\mu g\ kg^{-1}$ i.v. vecuronium, and anaesthesia was maintained with halothane and nitrous oxide along with 0.5 mg kg^{-1} of i.v. meperidine. A random number generator was used to assign each child prospectively to receive dexamethasone 1 mg kg^{-1} (maximum 25 mg), ondansetron 100 $\mu g\ kg^{-1}$ (maximum 4 mg) or saline placebo. The study drugs were prepared by an anaesthetist not otherwise involved in patient care, to a fixed volume of 5 ml, to maintain the double-blind nature of the study. Intraoperative i.v. fluid management consisted of administration of lactated Ringer's solution sufficient to correct half of the preoperative fluid deficit in the first hour, followed by maintenance fluids according to body weight. At the end of the procedure, residual neuromuscular blockade was antagonized with 50 $\mu g\ kg^{-1}$ of neostigmine and 10 $\mu g\ kg^{-1}$ of glycopyrrolate and the trachea was extubated when the child was awake. The gastric contents were aspirated by suction via a tube passed before extubation. No nasogastric tube was left *in situ* during the procedure.

After operation, all children were transported to the postanaesthesia care unit (PACU). The anaesthetist who provided intraoperative care assessed postanaesthetic recovery using the modified Aldrete scoring system.[4] Time to achieve complete recovery (score 10) was recorded for all children. After operation, analgesia was provided when older children complained or younger children cried in pain.[5] Oral ibuprofen 10 mg kg^{-1} was given as the analgesic of first choice, and for pain in children who had PONV in the immediate postoperative period in the PACU, ketorolac 0.5 mg kg^{-1} i.v. was administered as the analgesic of second choice by the anaesthetist who provided intraoperative care. Intravenous fluid comprised lactated Ringer's solution replacing the remaining fluid deficit plus maintenance fluids in the recovery room.

All episodes of nausea and vomiting in the first 24 postoperative hours in the hospital during the intervals of 0–6 h and 6–24 h were evaluated using a numeric scoring system for PONV (0=no nausea or vomiting, 1=nausea but no vomiting, 2=vomiting once in 30 min or more, 3= persistent nausea (>30 min) or two or more vomits in 30 min) by the PACU and ward nursing staff, who were aware of the nature of the study but blinded to the study drug. We did not assess nausea in very young children (less than 6 yr of age). In older children, nausea was assessed by an observer and by self-reporting. Any child having a PONV score of 3 was considered to have severe PONV and was treated with metoclopramide 150 $\mu g\ kg^{-1}$ i.v. as a rescue antiemetic. The time to achieve eligibility for fast tracking (fast tracking time, FTT) was calculated as the time from the discontinuation of anaesthesia to the time at which the child had a patent airway without support, no PONV, no pain and a recovery score of 10.

The criteria for discharge from PACU to ward included stable vital signs, adequate pain control and no nausea and vomiting in the first 2 h after surgery. Children who had PONV and pain in the first 2 h of stay were observed in PACU till they had remained free of PONV and pain for an hour.

Finally, at the end of 24 h after surgery, the primary caretaker was asked to give a global assessment of their satisfaction over the entire postoperative experience of the child (parental satisfaction score) using an 11-point verbal numeric scoring system (0=not at all satisfied, 10=fully satisfied).

Statistical analysis

Power analysis before the study showed that 41 children would be required in each group to have a 95% chance (β=0.05) of detecting a 50% relative reduction in PONV, from our Institute's basal incidence of 80%[6] with a type-1 error of 5% (α=0.05) and 95% confidence interval limits (Version 6.04b, Epi Info, Centre for Disease Control, Atlanta, GA, USA, and World Health Organization, Geneva, Switzerland, 1997). Two-sample *t*-tests and Mann–Whitney *U*-tests were used to compare the age, weight, duration of surgery, anaesthesia, recovery, fast tracking and PACU stay, perioperative fluid and analgesic requirements, and the parental assessment scores of the child's perioperative experience. The incidence and severity (requirement of rescue antiemetic) of PONV were compared by χ^2 and Fisher's exact tests with Yates' continuity correction wherever appropriate. The positive 'number needed to prevent' (NNTP) PONV (which indicates how many children had to be exposed to dexamethasone or ondansetron to prevent PONV) was calculated as the reciprocal of the absolute risk reduction of the incidences of PONV from the basal (placebo) incidence for children who received dexamethasone or ondansetron. The cost to benefit a child was calculated as the drug acquisition cost per patient times the NNTP for dexamethasone or ondansetron. *P*-values less than 0.05 were considered statistically significant, and data are presented as mean (SD) unless otherwise specified.

Results

Patient and clinical data, such as age, gender, weight, physical status, duration of surgery and anaesthesia, numbers of muscles operated, perioperative fluid, analgesic requirements and recovery time, were similar in all groups (Table 1).

Table 1 Demographic and clinical data. Sex, ASA status, previous PONV and oculocardiac reflex (OCR) are expressed as the number of children. Other values are expressed as mean (SD). All groups were statistically comparable

	Dexamethasone group (n=45)	**Ondansetron group** (n=45)	**Placebo group** (n=45)
Age (yr)	7.6 (3.8)	6.9 (3.5)	7.11 (2.91)
Sex (M/F)	21/24	18/27	23/22
Weight (kg)	20.6 (9.8)	21.9 (10.2)	20 (8.36)
ASA physical status (I/II)	44/1	43/2	41/4
Induction (halothane/thiopental)	33/12	28/17	31/14
Duration of surgery (min)	45.9 (21.7)	47.2 (10.9)	49.11 (16.83)
Recovery time (min)	15.4 (11.7)	15.9 (7.6)	20.4 (17.8)
Intraoperative			
fluids (ml kg^{-1})	16.7 (5.2)	16.2 (5.5)	18.1 (5.61)
analgesics (mg)	10.8 (4.9)	11.1 (5.1)	10 (5)
Previous PONV	2/45	4/45	4/45
OCR requiring atropine	4/45	5/45	6/45

Table 2 Incidence and severity of PONV. Values are expressed as the number (percentage) of children. **$P<0.05$ (dexamethasone versus ondansetron, dexamethasone versus placebo). Dexamethasone versus placebo: incidence and severity of PONV at 0–6 h ($P=0.0001$ and $P=0.0114$ respectively), 6–24 h ($P=0.0031$ and $P=0.0006$) and 0–24 h ($P<0.0001$ and $P=0.0000$). Ondansetron versus placebo: incidence and severity of PONV at 0–6 h ($P=0.0000$ and $P=0.0053$ respectively), 0–24 h ($P=0.0001$ and $P=0.0007$) and comparable incidence and severity at 6–24 h (P=0.4802 and $P=0.2277$) respectively

PONV outcome	**Dexamethasone group** (n=45)	**Ondansetron group** (n=45)	**Placebo group** (n=45)
PONV: incidence			
0–6 h	11 (24.4)	8 (17.8)	30 (66.7)
6–24 h	3 (6.7)	11 (24.4)	14 (31.1)
0–24 h	11 (24.4)	15 (33.3)	34 (75.6)
Nausea: 24 h incidence	1 (2.2)	6 (13.3)	19 (42.2)
PONV: score (0–24 h)			
0	34 (75.6)	30 (66.6)	11 (24.4)
1	0 (0)	1 (2.2)	0 (0)
2	3 (6.6)	1 (2.2)	5 (11.1)
3 (rescue antiemetic)	8 (17.8)	13 (28.9)	29 (64.4)
Rescue requirements (score 3)			
early (0–6 h)	8 (17.8)	7 (15.6)	19 (42.2)
late (6–24 h)	0 (0)**	6 (13.3)	10 (30.3)

The incidence of PONV was significantly greater in the placebo group than in the ondansetron ($P=0.0001$) and dexamethasone groups ($P<0.0001$) (Table 2). The incidences in the dexamethasone (24.4%) and ondansetron (33.3%) groups were comparable ($P=0.49$). The incidence of early PONV (0–6 h) was significantly lower in the ondansetron ($P<0.0001$) and dexamethasone groups ($P=0.0001$) than in the placebo group. The early incidence was comparable in the ondansetron (17.8%) and dexamethasone (24.4%) groups ($P=0.61$). The incidence of PONV in the late postoperative period (6–24 h) was significantly lower in the dexamethasone group (6.67%) than in the ondansetron (24.4%) ($P=0.04$) and placebo groups (31.1%) ($P=0.003$). The incidence of late PONV was comparable in the ondansetron and placebo groups ($P=0.48$). The incidences of PONV in children who were induced with halothane or thiopental in each group were comparable (Table 1).

The severity of early PONV was significantly lower in the ondansetron ($P=0.005$) and dexamethasone ($P=0.01$) groups compared with placebo. The severity of early PONV (requirement for rescue antiemetics) (0–6 h epoch) was comparable in the ondansetron (15.6%) and dexamethasone (17.8%) groups ($P>0.99$). The severity of late PONV (6–24 h epoch) was significantly less in the dexamethasone group (0%) than in the ondansetron (13.33%) ($P=0.03$) and placebo (30.3%) ($P=0.0006$) groups. The severity of late PONV in the ondansetron group was similar to that in the placebo group ($P=0.23$).

Recovery time was comparable in all groups. The FTT was similar in the ondansetron (28.4 (31.7) min) and dexamethasone (36.6 (44.5) min) groups ($P=0.67$). The FTT in the placebo group (67.5 (60.00) min) was significantly greater than that in the ondansetron ($P=0.0003$) and dexamethasone ($P=0.007$) groups. Duration of stay in the PACU was significantly longer in the placebo group (153.66 (41.41) min) than in the ondansetron ($P=0.0002$) and dexamethasone ($P=0.007$) groups, but comparable between the ondansetron and dexamethasone groups ($P=0.16$). The positive NNTP was comparable in the ondansetron (NNTP=2.36) and dexamethasone (NNTP=1.95) groups. The number of postoperative analgesic supplements in dexamethasone group (1.04 (0.7)) was significantly lower than in the ondansetron (1.7 (0.5)) and placebo (1.7 (0.7))

Table 3 True, therapeutic outcome measures and side-effects. NNTP PONV and side-effects are expressed as the number of children. Other values are expressed as mean (SD). Ondansetron and dexamethasone were statistically comparable for true, therapeutic outcome measures and side-effects. Ondansetron and dexamethasone groups had significantly higher parental satisfaction scores than the placebo group ($P<0.0001$). Both FTT and PACU stay were significantly longer in the placebo group than in the ondansetron ($P=0.0003$ and $P=0.0002$ respectively) and dexamethasone groups ($P=0.0068$ and $P=0.0074$)

PONV outcome	Dexamethasone group ($n=45$)	Ondansetron group ($n=45$)	Placebo group ($n=45$)
FTT (min)	36.6 (44.5)	28.44 (31.7)	67.46 (59.96)
PACU stay (min)	134.0 (24.7)	127.7 (17.2)	153.66 (41.14)
NNTP PONV	1.95	2.36	–
Side-effects			
Headache	3	4	2
Facial flushing	5	0	0
Wound problems	0	0	0
Parental satisfaction score	8.8 (1.6)	8.2 (1.6)	6.26 (2.24)

groups ($P=0.0000$) but comparable in the ondansetron and placebo groups ($P>0.99$). In the dexamethasone group, 11.1 and 7.1% of the children had facial flushing and headache respectively, and 8.8% of children in the ondansetron group had headache (Table 3). The parental assessment scores for the children's perioperative experiences were comparable in the dexamethasone and ondansetron groups ($P=0.08$). Children in the ondansetron and dexamethasone groups had significantly higher parental satisfaction scores than those in placebo group ($P<0.0001$).

The drug acquisition cost per patient was US$0.47 (0.50 euros) in the dexamethasone group and US$8.72 (9.26 euros) in the ondansetron group. The cost to benefit per patient (NNTP times the institutional drug acquisition cost) was 22.4 times higher in the ondansetron group than in the dexamethasone group.

Discussion

In children, strabismus repair is associated with a high incidence of PONV,[7] which ranges from 41 to 88% in those who have not received antiemetic prophylaxis.[8 9] Ondansetron had been shown to be effective in the prevention of PONV following strabismus repair.[10–12] However, a meta-analysis[1] has challenged the clinical utility of prophylactic ondansetron in preventing PONV on the basis of its efficacy and safety. Recently, prophylactic use of ondansetron at 75 $\mu g\ kg^{-1}$ has been shown to reduce the incidence of PONV from 80% to 30% and to improve the true outcome after strabismus repair in children.[6] However, the higher cost of ondansetron remains a major concern.

Dexamethasone has been shown to be an effective antiemetic in children undergoing ambulatory adenotonsillectomy.[3 13] Though the mechanisms of its antiemetic effects are still unclear, it may act through prostaglandin antagonism,[14] serotonin inhibition in the gut[15] and by releasing endorphins.[16]

In our study, the incidence of PONV was 33.3% in the ondansetron group, 24.4% in the dexamethasone group and 75.6% in the placebo group. Dexamethasone was as effective as ondansetron in decreasing the incidence and severity of PONV in the first 24 h after operation. The antiemetic efficacy of dexamethasone was most pronounced in the late postoperative period. The incidence and severity of PONV in the late postoperative period were significantly lower in the dexamethasone group than in the ondansetron and placebo groups. This prolonged antiemetic efficacy of dexamethasone may be explained by its prolonged biological half-life (36–72 h). Similar findings have been reported in patients undergoing ambulatory surgery.[13 17 18] Dexamethasone has been shown to provide greater protection from delayed chemotherapy-induced nausea and vomiting compared with ondansetron[19] and granisetron.[20]

In this trial, the groups were comparable with respect to patient characteristics, surgical procedure, anaesthetics administered and i.v. fluids used in the perioperative period. Therefore, the difference in the incidence and severity of PONV and true and therapeutic outcome measures among the groups in this trial can be attributed to the study antiemetics that were administered.

Betamethasone prophylaxis has been shown to decrease postoperative pain and late PONV in ambulatory surgical patients.[21] In our study, the requirement for postoperative analgesic supplements was significantly lower in the dexamethasone group. The antiemetic and analgesic effects of dexamethasone were more pronounced in the late postoperative period. This probably added to the comfort of the patients when they were discharged home.

In our trial, we used parental assessment scores of the child's perioperative experience, duration of PACU stay and fast tracking time as true outcome measures. Dexamethasone was as effective as ondansetron in improving true outcome measures in this group of patients.

We included a placebo group to allow us to calculate the absolute reduction in the risk of PONV, and thereby the NNTP. The NNTP indicates how many children need to be exposed to the treatment in order to prevent PONV in one of them. Meta-analyses have reported that the best NNTP with the well-documented regimens were between 4 and 6 for ondansetron[1] and 4 for dexamethasone.[22] In our trial, NNTP with dexamethasone (1 mg kg^{-1}) and ondansetron (100 μg kg^{-1}) was approximately 2. In the meta-analyses,[1 22] NNTP was reported to be greater possibly because of the heterogeneous patient population and defects in the meta-analyses of PONV.[6 23]

The timing of prophylactic antiemetic administration is important. We administered the drugs at the beginning of the procedure. It has been confirmed recently that dexamethasone is more effective when administered at induction than when given at the end of anesthesia.[24] Though it has been suggested that ondansetron given at the end of surgery will reduce antiemetic requirements more effectively in the postoperative period,[25] in short surgical procedures like strabismus surgery administering ondansetron at the beginning or end of surgery did not affect the outcome.[26]

In this pharmacoeconomic era, the cost to benefit a patient for prophylactic antiemetic is a significant factor. In the ondansetron group, the acquisition cost of drug per patient was 18.6 times higher than in the dexamethasone group. The cost to benefit a patient (i.e. NNTP times the cost of drug per patient) was 22 times higher in the ondansetron group than in the dexamethasone group. This reasserts the value of prophylactic dexamethasone as a cost-effective alternative to ondansetron.

Facial flushing was seen in five children (11%) after administration of dexamethasone. There were no associated haemodynamic changes in any of these patients. We requested the surgeons to inform us if any child was admitted with wound infection or delayed wound healing. There were no wound-related problems in any group. Headache was seen in three, four and two children in the dexamethasone, ondansetron and placebo groups respectively. Our sample size was inadequate to identify an adverse effect with an incidence of less than 2.2% (100/45). Meta-analysis may be effective in identifying adverse effects with low incidence. The recent meta-analysis on dexamethasone and PONV did not reveal any significant side-effects.[22] As yet, there is no evidence in the literature for dexamethasone's potential side-effects, such as hyperglycaemia, delayed wound healing and hypothalamic–pituitary adrenal axis suppression after a single dose.

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Comparison of effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients

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In a randomized double-blind study, we compared the effect of remifentanil and alfentanil on the cardiovascular response to laryngoscopy and tracheal intubation in patients on long-term treatment for hypertension. Forty ASA II–III patients were allocated to receive (i) remifentanil 0.5 $\mu g\ kg^{-1}$ followed by an infusion of 0.1 $\mu g\ kg\ min^{-1}$ or (ii) alfentanil 10 $\mu g\ kg^{-1}$ followed by an infusion of saline; all patients received glycopyrrolate 200 μg before the study drug. Anaesthesia was induced with propofol and rocuronium and maintained with 1% isoflurane and 66% nitrous oxide in oxygen. Laryngoscopy and tracheal intubation were performed after establishment of neuromuscular block. Arterial pressure and heart rate (HR) were measured non-invasively at 1 min intervals from 3 min before induction until 5 min after intubation. Systolic (SAP), diastolic and mean arterial pressure decreased significantly after induction in both groups ($P<0.05$). Maximum increases in mean SAP after laryngoscopy and intubation were 35 and 41 mm Hg in the remifentanil and alfentanil groups, respectively. After intubation, arterial pressure did not increase above baseline values in either group. HR remained stable after induction of anaesthesia, but increased above baseline values after intubation. Mean maximum HR was 87 beats min^{-1} for the remifentanil group (12 beats min^{-1} above baseline; $P=0.065$) and 89 beats min^{-1} for the alfentanil group (15 beats min^{-1} above baseline; $P<0.05$). There were no significant differences between groups in HR or arterial pressure at any time. There were no incidences of bradycardia. Seven patients in the remifentanil group and four in the alfentanil group received ephedrine for hypotension (i.e. SAP<100 mm Hg).

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Laryngoscopy and tracheal intubation may be accompanied by hypertension, tachycardia and raised intracranial pressure and can be associated with myocardial ischaemia in susceptible individuals.[1] This response may be exaggerated in patients with treated or untreated essential hypertension[2] who have a greater incidence of coexisting coronary artery and cerebrovascular disease. Many drugs have been shown to be effective in modifying this haemodynamic response in healthy patients, including remifentanil[3] and alfentanil.[4 5] Remifentanil is an opioid drug with a pharmacological profile ideal for the treatment of brief noxious stimuli.[6 7] Few studies of the haemodynamic response to intubation have been carried out in hypertensive patients or those at risk of developing myocardial ischaemia[8] and none have used remifentanil. In this randomized double-blind study, we compare the relative efficacy of remifentanil with that of alfentanil in modifying the haemodynamic response to intubation in patients receiving long-term treatment (>6 months) for hypertension.

Patients and methods

After hospital ethics committee approval and informed consent, 40 ASA II–III patients aged 33–78 yr, receiving long-term treatment (>6 months) for hypertension and undergoing elective surgery requiring tracheal intubation were recruited. They were allocated at random to two groups using a sealed envelope technique. Criteria for exclusion were: ASA grade III or greater; hiatus hernia or significant gastro-oesophageal reflux; obesity (body mass

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Table 1 Patient characteristics: mean (SD or range) or number. Baseline arterial pressures and heart rate are the mean of three values taken immediately before induction of anaesthesia

	Remifentanil (n=20)	Alfentanil (n=20)
Age (yr)	64 (33–78)	63 (49–78)
Gender (male/female)	10/10	10/10
Weight (kg)	76.2 (14.7)	77.0 (11.9)
Propofol dose (mg)	95.3 (26.3)	95.3 (24.8)
Baseline arterial pressure (mm Hg)		
SAP	159 (26)	162 (20)
MAP	106 (19)	111 (15)
DAP	85 (15)	88 (10)
Baseline heart rate (beats min^{-1})	75 (14)	74 (12)
Duration of laryngoscopy (s)	17.5 (13)	21.0 (16)

Table 2 Concurrent antihypertensive medication and requirements for escape medication, according to treatment group; figures in brackets refer to the numbers of patients who required ephedrine to treat hypotension (SAP<100 mm Hg)

	Remifentanil (n=20)	Alfentanil (n=20)
Diuretic	1	2 (1)
Beta blocker	2 (1)	4 (1)
ACE inhibitor	3 (2)	1
Calcium channel blocker	4	3
Combination therapy	10 (4)	10 (2)

index >30); anticipated difficulty with airway maintenance or intubation; recent myocardial infarction, congestive cardiac failure or ECG evidence of heart block; or the presence of a cardiac pacemaker.

Patients were not premedicated and received their usual antihypertensive drugs on the day of surgery. All patients received Hartmann's solution 5 ml kg^{-1} over 5–10 min before induction of anaesthesia. Patient's lungs were pre-oxygenated for 3 min and glycopyrrolate 200 µg i.v. was administered followed by the study drug and by an infusion, as described below.

At induction of anaesthesia, group 1 (n=20) received a bolus of remifentanil 0.5 µg kg^{-1} over 30 s followed by an infusion of remifentanil at 0.1 µg kg^{-1} min^{-1}. Group 2 (n=20) received a bolus of alfentanil 10 µg kg^{-1} over 30 s followed by an infusion of saline at the same rate. Infusions of remifentanil (group 1) and saline (group 2) continued throughout the study period. All study drugs and infusions were prepared by a third party, so that the investigators were unaware of their identity.

Immediately after the bolus of study drug, a standard general anaesthetic was administered, comprising propofol 0.5 mg kg^{-1} followed by 10 mg every 10 s until loss of verbal contact, and rocuronium 0.6 mg kg^{-1} to produce neuromuscular block. Patients' lungs were ventilated manually using a Bain circuit with 1% isoflurane and 66% nitrous oxide in oxygen, to an end-tidal carbon dioxide tension of 4.0–4.5 kPa using a Datex Capnomac. After establishment of neuromuscular blockade, confirmed with a nerve stimulator (Fisher Paykell NS272), laryngoscopy and orotracheal intubation were performed, 3 min after induction.

Heart rate (HR) and systolic, mean and diastolic arterial pressures (SAP, MAP and DAP) were recorded at 1 min intervals from pre-oxygenation to 5 min after intubation. Arterial pressure was measured non-invasively using an automatic oscillometric device (Datex Cardiocap) and ECG was monitored with electrodes in the CM5 position. The duration of laryngoscopy and any difficulties in laryngoscopy or tracheal intubation were noted.

Escape medication (ephedrine 3 mg increments) was administered for hypotension (SAP<100 mm Hg, or a decrease of >30% of baseline for >60 s) and atropine, in 300 µg increments, for bradycardia (HR<45 beats min^{-1}). For hypertension (SAP>200 mm Hg, or an increase of >30% above baseline values, for >60 s) or tachycardia (HR>130 beats min^{-1} for >60 s), the inspired isoflurane concentration was increased in increments of 0.5%. Power analysis, based on previous data,[3] suggested that 20 patients per group would give an 80% chance of detecting a difference between the groups of 15 mm Hg in the cardiovascular response to intubation. (α=0.05, β=0.2). Statistical analysis was performed using general linear model analysis of variance for repeated measures (with treatment group and time as between- and within-group factors, and Bonferroni testing to adjust for multiple comparisons of each parameter) using SPSS for Windows computer software (release 9.0, 1998).

Results

Patient characteristics, baseline haemodynamic variables (SAP, DAP, MAP and HR) and antihypertensive medication were similar between groups (Tables 1 and 2). There were significant changes over time in SAP, DAP, MAP and HR (P<0.001) but no difference at any time between groups. Changes in mean SAP, MAP and DAP occurred in parallel and are therefore reported together. Arterial pressure decreased significantly after induction of anaesthesia in both groups (P<0.05 within groups), but there was no significant change in mean HR in either group (Table 3).

SAP, MAP and DAP after intubation were significantly higher (P<0.05) than those before intubation. The increases in SAP and DAP were sustained for 4 min after intubation in the alfentanil group and for 2 min in the remifentanil group. The greatest mean increase in SAP occurred 2 min after intubation in both groups (34 and 41 mm Hg in remifentanil and alfentanil groups, respectively). However, SAP in both groups remained below pre-induction values throughout the study period (P<0.05 from 4–5 min after intubation). DAP and MAP after intubation were also significantly higher (P<0.05) than those before intubation, increasing towards baseline values in both groups, but they then decreased and values were significantly lower than baseline from 4–5 min after intubation (P<0.05).

Table 3 Mean (SD) values of heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure; *P<0.05 compared with baseline; †P<0.05 compared with pre-intubation values

	Baseline	After induction	Before intubation	+1 min	+2 min	+3 min	+4 min	+5 min
Remifentanil								
SAP (mm Hg)	159 (26)	129* (33)	104* (32)	134† (26)	138† (23)	126* (23)	115* (22)	108* (22)
DAP (mm Hg)	84 (15)	71* (18)	59* (15)	82† (17)	78† (16)	69 (14)	62* (13)	59* (14)
MAP (mm Hg)	106 (19)	87* (22)	74* (18)	100† (17)	95† (18)	84 (17)	77* (15)	74* (15)
HR (beats min^{-1})	75 (14)	75 (15)	72 (14)	87† (12)	83† (11)	79 (12)	76 (13)	75 (14)
Alfentanil								
SAP (mm Hg)	162 (18)	133* (32)	103* (28)	136† (36)	144† (34)	136† (29)	125*† (24)	121* (26)
DAP (mm Hg)	88 (10)	70* (19)	57* (16)	90† (27)	87† (21)	81† (14)	73*† (14)	70*† (15)
MAP (mm Hg)	111 (15)	84* (20)	72* (21)	105† (32)	105† (24)	98† (16)	89* (17)	86* (19)
HR (beats min^{-1})	74 (12)	74 (17)	70 (15)	89*† (19)	87*† (16)	82† (15)	80† (14)	79† (15)

Changes in HR after induction of anaesthesia were minimal, but there was a significant increase in HR after intubation in both groups (P<0.05). Mean maximum HR occurred 1 min after intubation in both groups, and was 87 beats min^{-1} (12 beats min^{-1} above baseline; P=0.065) in the remifentanil group and 89 beats min^{-1} (15 beats min above baseline; P<0.05) in the alfentanil group. However, there were no overall differences between groups for SAP, DAP, MAP or HR.

Seven patients in the remifentanil group and four in the alfentanil group required ephedrine 3–9 mg to treat hypotension (SAP<100 mm Hg). Marked hypotension (SAP<80 mm Hg for >1 min) occurred in three patients in the remifentanil group and two in the alfentanil group. There was no clear relationship between type of antihypertensive medication and requirement for escape medication (Table 2). Three patients in the alfentanil group and none in the remifentanil group required an increase in the inspired concentration of isoflurane to treat hypertension. A SAP of >200 mm Hg occurred in only one patient in the alfentanil group. Data from all patients, including those who required escape medication, were analysed. No patient required treatment for bradycardia. Transient ST segment depression associated with tachycardia occurred after intubation in one patient in the remifentanil group. This resolved spontaneously within 3 min without specific treatment. No other ST segment changes were observed.

Discussion

We found that the effect of a bolus dose of remifentanil 0.5 μg kg^{-1} followed by a 0.1 μg kg^{-1} min^{-1} infusion was similar to that of a 10 μg kg^{-1} bolus of alfentanil in controlling the haemodynamic response to intubation in treated hypertensive patients. Although arterial pressure increased after intubation in both groups, values remained below baseline. HR after intubation was higher than that before intubation in both groups but the increases in HR and arterial pressure were not considered clinically significant. The increase in HR above pre-intubation values was sustained for 2 min after intubation in the remifentanil group, and for 5 min in the alfentanil group. This is probably because the remifentanil was being administered by intravenous infusion whereas, after only a single bolus dose, plasma and effect-site alfentanil concentrations would have been declining by this time.[9]

We have recently shown that in young adults a bolus dose of remifentanil 0.5 μg kg^{-1} followed by an infusion at 0.25 μg kg min^{-1} is as effective as a remifentanil bolus of 1.0 μg kg^{-1} followed by an infusion at 0.5 μg kg min^{-1}, in attenuating the haemodynamic response to intubation.[10] The increase in SAP, DAP and MAP after intubation in young adults was approximately 10 mm Hg, compared with 30 mm Hg in the present study. This may reflect the fact that hypertensive patients demonstrate a greater cardiovascular response to laryngoscopy and orotracheal intubation, but could be related to the lower infusion regimen used in this study. However, the incidence of hypotension observed in the present study (7/20 patients in the remifentanil group required escape medication for hypotension) implies that higher doses of remifentanil would have been inappropriate in this patient population.

Previous studies have shown an unacceptable incidence of bradycardia associated with the use of remifentanil in the absence of a vagolytic drug.[3] In this study, glycopyrrolate 200 μg was given before induction of anaesthesia and no patient required treatment for bradycardia. Seven patients in the remifentanil group and four in the alfentanil group were treated for hypotension. In most cases the hypotension was moderate (i.e. SAP>80 mm Hg) and responded well to small doses of ephedrine. The incidence of hypotension in this study confirms the view that hypertensive patients demonstrate exaggerated swings in arterial pressure and HR in response to induction of anaesthesia and tracheal intubation.[2] However, hypotension occurred despite i.v. fluid preloading and glycopyrrolate, and may have been related to the use of propofol in combination with remifentanil or to the effects of antihypertensive medication.

Bolus doses of alfentanil 10–15 μg kg^{-1} have previously been shown to be effective in modifying the cardiovascular response to intubation.[4 5] Higher doses of alfentanil ($\leq$40 μg kg^{-1}) have been used in some studies, but these were in healthy young adult patients and such doses have been associated with bradycardia and hypotension.[4] In elderly patients, a dose of alfentanil 10 μg kg^{-1} was effective,[11] so this dose was chosen for our study. Pharmacokinetic modelling indicates a 20- to 30-fold greater potency for remifentanil than for alfentanil.[12] A bolus dose of alfentanil 10 μg kg^{-1} approximates to remifentanil 0.5 μg kg^{-1} based on relative potencies of 20:1. We chose a lower infusion rate of remifentanil than in our previous study because in the elderly the clearance and volume of distribution of remifentanil are reduced, and the pharmacodynamic effects are greater.[13] The similarity in results between the two groups suggests that the doses of remifentanil and alfentanil chosen were comparable.

Recent data have again highlighted the problem of hypotension after induction of anaesthesia in patients receiving antihypertensive medication, in particular angiotensin-converting enzyme (ACE) inhibitors.[14] A possible criticism of this study is that the patients were receiving different types of antihypertensive medication, and this was not controlled between groups. However, Sear and colleagues found no difference in the cardiovascular response to intubation in patients receiving different monotherapies for mild to moderate hypertension,[15] and the distribution of type of antihypertensive medication between groups in this study was similar. Furthermore, the aim of this study was to establish whether remifentanil was as effective as alfentanil in a cohort of hypertensive patients, rather than examine the effects in those taking particular types of antihypertensive drugs. Although no firm conclusions can be made from a study of this size, escape medication for hypotension was required by patients taking beta blockers, ACE inhibitors, diuretics and combination therapy, with no clear association between type of antihypertensive treatment and hypotension after induction of anaesthesia. Further studies might assess the effects of opioids and specific antihypertensive medication.

This study supports the notion that hypertensive patients have an exaggerated cardiovascular response to laryngoscopy and tracheal intubation and are susceptible to episodes of hypotension after induction of anaesthesia. The occurrence of transient ST depression despite treatment measures confirms that this group is at risk of myocardial ischaemia. In conclusion, remifentanil and alfentanil in the doses described were similarly effective in reducing the cardiovascular response to laryngoscopy and orotracheal intubation.

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Comparison of coagulation and blood loss during anaesthesia with inhaled isoflurane or intravenous propofol

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Propofol has been reported to affect blood coagulation. This prospective, randomized study compared coagulation and blood loss during anaesthetic maintenance with target-controlled intravenous propofol infusion *vs.* inhaled isoflurane. Thirty-eight ASA I–III patients undergoing head and neck surgery were allocated randomly to receive either inhaled isoflurane at end-tidal concentration 1–1.5% (group I, n=20) or target-controlled infusion (TCI) of propofol at target concentration 2–5 $\mu g\ ml^{-1}$ (group P, n=18). Thrombelastography® on recalcified whole blood was performed pre-induction, and at 15, 30, 60, 90, 120 min post-induction and 30 min after anaesthesia in both groups. Blood loss was estimated from weighing swabs and the volume in suction bottles. Induced hypotension was not used, and perioperative body temperature was similar between groups. There were no significant differences in thrombelastographic coagulation (R-time, K-time, maximum amplitude and angle) or fibrinolytic variables (lysis index at 30 and 60 min) at all times between groups. Total blood loss was also not significantly different (median group I: 350 ml, range 20–1200 ml; group P: 200 ml, range 50–800 ml). Shortening of R-time and widening of angle developed over time in both groups (P<0.05 groups I and P, repeated measures ANOVA). We conclude that maintenance of anaesthesia with propofol TCI at 2–5 $\mu g\ ml^{-1}$ does not cause detectable coagulation changes on thrombelastography® nor increase surgical blood loss when compared to inhaled isoflurane.

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The use of intravenous (i.v.) propofol infusion for maintenance of anaesthesia is gaining in popularity, particularly with the introduction of commercial target-controlled infusion (TCI) systems. A number of recent studies have raised the concern that propofol may have adverse effects on blood coagulation and fibrinolysis[1–4] and, particularly, impair platelet aggregation.[1–3] The lipid emulsion solvent of propofol may also affect platelet function.[5 6] Such data would suggest that the use of propofol infusion for anaesthetic maintenance might be undesirable in operations where bleeding may become a problem. However, previous studies on propofol and coagulation were performed *in vitro*[1 3 4] except one *in vivo* study,[2] where no coagulation measurement was made during propofol infusion. It has also been shown that some inhaled agents may have inhibitory effects on coagulation.[1 7 8] In this study, we decided to investigate the effects of propofol on coagulation under three conditions that we feel are more clinically relevant: (1) *in vivo* during surgery with ongoing infusion of propofol; (2) with propofol administered in its usual form, that is dissolved in its lipid emulsion solvent; and (3) not looking at the coagulation effects of propofol in isolation, but comparing it with an alternative for anaesthetic maintenance, inhaled isoflurane.

Methods

The investigation was approved by the Institutional Research Ethics Committee. With informed written consent, ASA I–III patients scheduled for elective head and neck operations were recruited. These patients were undergoing resection of head and neck tumours followed by reconstructive plastic surgery. Those with a history of abnormal bleeding, or with abnormal preoperative prothrombin time, activated partial thromboplastin time or platelet count or who were taking drugs that may affect coagulation were excluded. Patients who required fibreoptic intubation prior to induction of anaesthesia were also excluded.

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Eligible patients were allocated randomly to one of two groups: group I, maintenance of anaesthesia with inhaled isoflurane at an end-tidal concentration of 1–1.5%; group P, maintenance of anaesthesia with TCI propofol (1% prefilled syringe AstraZeneca, UK) using a Diprifusor® pump (Graesby, UK) with a target plasma concentration of propofol between 2 and 5 μg ml^{-1}. Patients were unpremedicated and anaesthesia was induced in both groups using i.v. fentanyl 2–2.5 μg kg^{-1} and propofol 2–2.5 mg kg^{-1}. Rocuronium was administered for neuromuscular block and continued according to response to train-of-four peripheral nerve stimulation. Patients' tracheas were intubated and lungs mechanically ventilated throughout surgery to an end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) between 4–5 kPa. Morphine was used for analgesia and both groups also received 30% oxygen in nitrous oxide. At the end of surgery, all patients had their neuromuscular block antagonized and resumed spontaneous breathing via either a tracheostomy or their natural airway. Continuous pulse oximetry, electrocardiogram, $P\text{E}'_{CO_2}$, end-tidal anaesthetic agent, radial arterial pressure and core temperature were monitored throughout the operation. All i.v. fluids were warmed, and a warm air blanket (Bair Hugger 505®, Augustine Medical Inc., MN, USA) was applied to every patient unless it caused interference to the surgical field. There was no induced hypotension and patients' systolic arterial pressures were maintained at 100 mm Hg or 70% of the preoperative value, whichever was higher. Hypotension was treated with i.v. crystalloid fluid loading or intravenous boluses of ephedrine as appropriate.

The variables to be observed or measured in this study were: (1) serial thrombelastography® (TEG®); (2) intraoperative blood loss; (3) serial body temperature; and (4) patient characteristics and surgical details. Whole arterial blood samples were taken for TEG® measurement (CTEG® model 3000, Haemoscope Corporation, Skokie, IL, USA) before induction and at 15, 30, 60, 90 and 120 min after induction. The last sample was taken in the recovery room 30 min after the patient first opened their eyes to verbal command. Blood samples were collected with the double syringe technique[9] from the radial arterial line. The first 6 ml of each sample was discarded. Samples of whole blood (3.5 ml) were then collected in a bottle containing 3.2% sodium citrate (blood to citrate 1:9 by volume; Vacuette®, Greiner GmbH, Germany) and stored at room temperature until measurement. Because of the limited number of TEG® channels available, there were slight variations in the exact measurement time for individual samples. Recalcification was performed immediately before measurement by adding 15 μl of 0.2 M calcium chloride solution to 335 μl of whole blood from the citrate bottle.[9] Mixing was accomplished by lowering the piston of the TEG® into the plastic cup 10 times. No celite was added for the TEG® measurement and all measurements were made within 3 h of sample collection. All conventional TEG® variables including R-time, K-time, maximum amplitude (MA), angle (α), and lysis index at 30 (LY30) and 60 (LY60) min were recorded.

Total blood loss was recorded at the end of surgery by measuring the volume collected in the suction bottles and weighing swabs collected from the operative field.

Statistics and power analysis

Statistical analysis was performed using the software programme Statistica release 4.5 (StatSoft®, Tulsa, OK, USA). Intergroup comparisons of parametric data such as the TEG® parameters, volume of fluids administered and body temperature were performed using two-tailed unpaired *t*-test at each time point of observation. Blood loss was compared using the Mann–Whitney *U* test. The change in various TEG® variables over time was compared to the preoperative value in each group by repeated measures ANOVA. Where a statistically significant difference was detected, further pairwise comparisons were made between individual time points and the preoperative values using two-tailed paired *t*-test. The significance level was set at a *P* value of <0.05.

Based on our previous experience, the average blood loss in these procedures was around 400 ml. A sample size of 20 patients in each group would give us an 80% power to detect a difference in blood loss of 100 ml between the two groups, assuming the standard deviation of blood loss would be around 120 ml and at the current α-error level. This sample size would also have more than 80% power to detect the magnitude of propofol related fibrinolysis reported by Kohro and colleagues.[4]

Results

A total of 40 patients were recruited. However, only the data from 38 patients were used for analysis, as there were two patients in whom data collection was incomplete. There were 20 patients in group I and 18 patients in group P. Patient details and surgical information is displayed in Table 1.

It has been previously reported that during maxillary sinus surgery, blood loss is significantly correlated to body weight and operation duration.[10] We have, therefore, compared total blood loss, and blood loss adjusted for patients' body weight and total operation time between the two groups. There was no statistically significant difference in blood loss between the two groups (Fig. 1), although blood loss in group I tended to be slightly higher (median total blood loss group I: 350 ml, range 20–1200 ml; group P: 200 ml, range 50–800 ml).

There were also no statistically significant differences in any TEG® variables, including clotting parameters (R-time, K-time, MA and α) and fibrinolytic (LY 30 and LY 60) variables between the two study groups at all time points after induction of anaesthesia. The rate of clot formation was increased in both groups, with shortening of R-time and

K-time and widening of α, as time progressed (group I: $P<0.05$ for R-time and α; group P: $P<0.05$ for R-time, K-time and α, repeated measure ANOVA). These results are displayed in Table 2. There was no difference in body temperature between the two groups at all measurement points.

Table 1 Patient characteristics (mean (SD) or actual numbers). No significant differences between groups

	Group 1	Group P
Age	53.9 (19.6)	49.2 (15.5)
Weight (kg)	54.1 (10.5)	56.1 (8.6)
Height (m)	1.6 (0.1)	1.7 (0.1)
Body mas index (kg m^{-2})	20.4 (2.8)	19.7 (2.6)
Platelet count (×10^9 litre^{-1})	239 (104)	229 (58)
Sex ration (M/F)	12/8	10/8
Smoking (Y/N)	13/7	14/4
Cancer (Y/N)	16/4	11/7
Liver/renal disease (Y/N)	0/20	1/17
Diabetes (Y/N)	2/18	0/18
Duration of operation (min)	217 (106)	208 (135)
Inraoperative fluids administered		
Crystalloids (litre)	1.71 (1.02)	1.56 (1.06)
Colliods (litre)	0.31 (0.43)	0.19 (0.31)
Packed cells (unit)	0.12 (0.49)	0.13 (0.50)

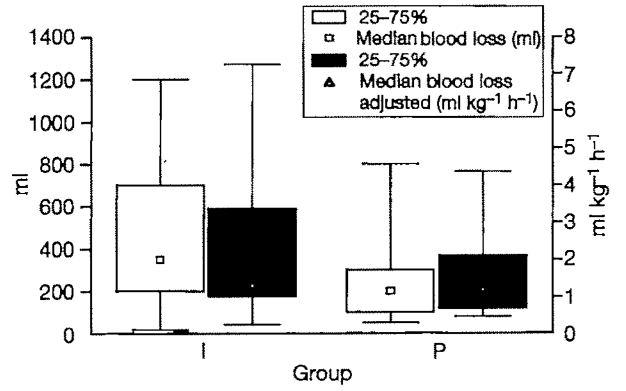

Fig 1 Total blood loss and blood loss per kg body weight per hour of operation. There were no significant between group differences (P=0.185 for total blood loss; P=0.274 corrected for body weight and operation duration. Mann–Whitney *U* test).

Discussion

The pharmacokinetic properties and recovery characteristics of propofol have encouraged its use for i.v. maintenance of anaesthesia. There are, however, a number of studies showing that propofol has an inhibitory effect on coagulation and platelet aggregation and that it enhances fibrinolysis.[1–4] The lipid emulsion solvent of propofol may also affect platelet function.[5 6] It is possible, therefore, that the benefits of infusing propofol dissolved in lipid emulsion for maintenance of anaesthesia during delicate neurosurgical or ophthalmological procedures may be offset by the potential risk of increased bleeding. However, the studies which have demonstrated the adverse effects of propofol on coagulation were mostly *in vitro* studies,[1 3 4] or were referring to propofol concentrations higher than that usually maintained in patients' plasma.[1 3 4]

In this investigation we have attempted to determine the existence, or otherwise, of such a potential risk by using a prospective randomized trial comparing anaesthetic maintenance with i.v. propofol dissolved in lipid emulsion and that with a conventional inhaled agent. We chose isoflurane for comparison in our study not only because it is popular, but also because many other inhaled agents such as halothane and sevoflurane have been shown to have antiplatelet or other adverse coagulation effects themselves.[1 7 8 11–13] Isoflurane has not been found to possess these properties. Anaesthetic induction was accomplished by i.v. propofol in both groups as the airway irritant effect of isoflurane made this agent undesirable for this purpose. With an initial fast distribution half-time of around 3 min,[14] the initial bolus of propofol is unlikely to have affected the first intergroup comparison at 15 min post-induction.

One of the limitations of previous studies investigating the coagulation effects of propofol is the lack of control over

Table 2 Change of TEG® parameters over time (mean (SD)). *$P<0.05$ compared with preoperative value (ANOVA); normal ranges R: 15–23 mm; K: 4–15 mm; MA: 34–46 mm; α: 36–48° (Operator's manual, TEG®, Haemoscope Corp.)

	Preoperative	15 min	30 min	60 min	90 min	120 min	Postoperative
Group I (n=20)							
R	15.03 (5.48)	17.03 (5.70)	17.00 (4.65)	15.68 (3.58)	15.37 (2.50)	15.30 (3.23)	12.42 (3.07)*
K	7.13 (4.76)	5.53 1.94)	5.55 (2.81)	5.74 (3.48)	5.50 (2.84)	5.03 (2.21)	4.44 (1.55)
MA	52.85 (6.66)	53.15 (6.79)	54.79 (8.55)	53.42 (7.34)	53.71 (8.28)	54.00 (4.61)	51.31 (12.28)
α	55.15 (15.67)	57.08 (8.72)	58.47 (12.07)	58.42 (12.83)	59.29 (10.15)	61.07 (9.81)	61.53 (13.09)*
LY 30	0.84 (1.12)	1.10 (0.87)	1.47 (1.49)	1.58 (2.14)	1.28 (1.43)	1.15 (1.01)	0.89 (0.94)
LY 60	2.23 (2.62)	2.77 (1.24)	3.44 (2.13)	2.87 (2.88)	3.18 (2.19)	2.58 (2.49)	2.05 (1.82)
Group P (n=18)							
R	18.72 (4.08)	16.89 (6.60)	15.76 (5.30)	15.81 (3.36)*	17.42 (4.44)	16.81 (5.90)	14.06 (4.62)*
K	7.53 (4.25)	5.92 (3.64)*	5.18 (3.57)*	5.50 (2.89)*	5.69 (3.40)*	5.73 (3.11)*	5.29 (1.95)*
MA	53.75 (9.58)	52.83 (7.31)	53.79 (6.77)	54.37 (5.62)	55.73 (7.49)	56.42 (10.39)	56.21 (8.35)
α	51.97 (14.00)	58.03 (12.91)	61.79 (12.51)*	57.88 (12.33)	57.96 (13.49)*	58.42 (13.85)*	59.24 (8.96)*
LY 30	1.89 (3.30)	1.41 (2.80)	1.37 (1.51)	1.46 (1.41)	2.12 (4.10)	0.85 (0.41)	0.75 (0.68)
LY 60	4.05 (5.18)	4.10 (5.38)	3.00 (3.12)	3.45 (1.91)	4.13 (4.67)	2.22 (1.28)	2.23(1.67)

the actual plasma concentration of propofol during the time of measurement. During *in vitro* studies, propofol or intralipid was usually only administered at a fixed rate[15 16] or as a single bolus.[17] The concentrations of propofol used during *in vitro* studies, were usually well above those administered to maintain anaesthesia clinically.[3 4] TCI systems, such as the Diprifusor®, use a pharmacokinetic model to predict the initial bolus dose and infusion rates to achieve and maintain a given target blood propofol concentration. There is good evidence to show that the bias and inaccuracy of this system are reasonably low and the predicted concentration correlates well with the actual plasma level.[18] Our results should be an accurate reflection of the changes that might occur during normal use of this drug.

Most studies on the effect of propofol on coagulation have identified an inhibitory effect of propofol on platelet aggregation[1–3] or an enhancement of fibrinolysis[4] as the underlying mechanism. Although platelet aggregometry is an excellent tool for monitoring platelet aggregation, it requires a large sample volume for measurement and is time consuming. It was, therefore, not desirable in our study where repeated measurements were necessary on the same patient. Moreover, changes in platelet function as seen on aggregometry may not necessarily correlate with changes in surgical blood loss.[19 20] In contrast, the TEG® is a simple bedside tool which allows rapid measurement of global coagulation including fibrinolysis with a relatively small sample volume. TEG® has been reported to predict blood loss in a variety of procedures,[21–23] and has also been used successfully to identify the coagulation effects of propofol.[4] We believe, therefore, that it is an appropriate coagulation monitor for this study.

There was no difference observed in TEG® variables between the two groups of patients during the first 2 h of anaesthesia and at the end of surgery in our study. We also did not find any difference in blood loss either in terms of absolute value, or adjusted to patients' body weight and operation duration. Despite the *in vitro* evidence of propofol's adverse effects on coagulation, propofol does not appear to increase blood loss during surgery. There were studies which showed *less* blood loss where propofol anaesthesia was compared with maintenance with inhaled agents for endoscopic sinus surgery, both retrospectively[15] and in a prospective randomized study.[16] Propofol maintenance was also associated with reduced blood loss for termination of pregnancy,[24 25] although this may be related to its effects on uterine muscle. Propofol *vs.* inhaled agent maintenance gave rise to similar blood loss during Caesarean section.[26] Although there was no statistically significant difference in blood loss between the two groups in our study blood loss did tend to be slightly higher in the isoflurane group. With the support of the TEG® findings and the elimination of possible confounders, such as intergroup differences in arterial pressure or body temperature in our study, we conclude that i.v. maintenance of anaesthesia with propofol does not adversely affect coagulation to a clinically significantly extent, as compared to use of isoflurane.

The results of early *in vitro* studies strongly suggest that propofol possesses antiplatelet properties.[1–3] A recent study, however, indicated that the effect of propofol might differ in high and low concentrations.[27] In particular, the results of this study suggested propofol might enhance secondary aggregation by ADP and epinephrine at concentrations around 5 μg ml^{-1}. This could partly explain the different observations in our study compared with earlier *in vitro* studies. Another issue which is relevant to our study, and other *in vivo* studies, is the natural development of a hypercoagulable state associated with surgical stress and tissue trauma.[28 29] This was suggested in our study by shortening of R-time, K-time and widening of α in most samples collected intra- and postoperatively in both groups. The antiplatelet and profibrinolytic effects of propofol are probably mild at the concentrations used clinically, and will not be detectable with the development of such natural hypercoagulability. However, it is important to note that the changes in TEG® variables over time in both groups in our study may not be totally attributable to 'real' hypercoagulability. Shortening of R- and K-time, and widening of α have been demonstrated to occur in recalcified citrated blood over time[30] and would contribute to at least part of the changes observed. However, this should not have affected the validity of intergroup comparisons. In any particular patient, the delay in measurement was related to the time required to complete measurement of a previous sample. As a result, although there should be more delay in the recovery room sample as compared with the pre-induction sample for example, the delay at any particular sampling point should be similar.

We conclude that maintenance of anaesthesia with i.v. infusion of propofol dissolved in lipid emulsion at target concentrations of 2–5 μg ml^{-1} is not associated with increased risk of bleeding compared with maintenance with inhaled isoflurane. We believe that the use of this technique is safe even during procedures where an increased risk of bleeding should be strictly avoided, provided patients do not have other conditions that may interfere with coagulation. Further studies are required to investigate the long-term effect of propofol infusion, such as for sedation in ICU, the safety of using propofol in the presence of other drugs that are known to have an inhibitory effect on coagulation such as non-steroidal anti-inflammatory agents and heparin, and the effect of propofol in patients with disorders of haemostasis.

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Decontamination of laryngoscopes in The Netherlands

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In this study the decontamination procedures of laryngoscopes in Dutch hospitals are described, based on a structured telephone questionnaire. There were substantial differences between decontamination procedures in Dutch hospitals and the standards of the APIC (Association of Professionals in Infection Control and Epidemiology), CDC (Centers of Disease Control) and ASA (American Society of Anesthesiology) were met in full in 19.4% of the hospitals. The standards of manual decontamination, used in 78% of the 139 hospitals, were particularly disappointing; manual cleaning was considered inadequate in 22.9% of these hospitals and manual disinfection did not meet the standards of the APIC, CDC or ASA in any of these hospitals. Decontamination by instrument cleaning machines as a standard procedure was used in 30 (22%) hospitals. In three of these hospitals the blades were subsequently sterilized. We suggest adherence to the infection control guidelines of the CDC, APIC and ASA, until the safety of less conservative infection control practices are demonstrated.

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The importance of appropriate disinfection of equipment for preventing infection has been emphasized.[1] However, Esler[2] in a recent survey of decontamination of laryngoscopes in the United Kingdom (UK) concluded that 'there appears to be no rationale regarding the aim of laryngoscope cleaning or agreed methods to achieve that aim'. The results of this and other studies,[3 4] and the culture results of our own laryngoscope blades considered ready for use, provided the basis to study the decontamination procedures of laryngoscopes in The Netherlands.

For a decontamination procedure to be appropriate, the equipment should first be thoroughly cleaned. A process in which all organic matter and other residues are removed using water, mechanical action, and detergents or enzymatic products.[5 6] Subsequently, disinfection or sterilization should be performed; disinfection describing a process that eliminates many or all pathogenic micro-organisms, with the exception of bacterial spores, from inanimate objects.[6 7]

Therefore, to assess the procedures for decontamination of larygoscopes, it should be known how both cleaning and disinfection/sterilization are carried out and whether or not the correct sequence is followed. Unfortunately, these processes have not been adequately described in previous studies. In addition, the use of a postal questionnaire as a tool to acquire this information, is in our opinion, too restrictive and may have a negative impact on the validity of the results. The aim of this study was to assess laryngoscope decontamination procedures in The Netherlands and to compare them with current guidelines.

Methods

The decontamination procedure in our hospital at the time of this study consisted of manual cleaning by brushing or wiping using a detergent and rinsing under running water followed by disinfection by wiping with a gauze soaked in ethanol 70%. The decontamination procedures in the other 138 Dutch hospitals were studied by means of a structured telephone questionnaire (Appendix A) asking open questions if possible. During the first 15 interviews, the questionnaire was adjusted if necessary. If data were missing or if there was doubt about the answers, the hospitals were contacted again within 1 week. If machines were used during the decontamination process, the hospital's central sterilization department was contacted in order to obtain information on the details of the process.

Manual cleaning was considered adequate when all of the following criteria in every case were fulfilled: (1) the blade was brushed or wiped, (2) a detergent or enzymatic agent

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was used, and (3) the blade was rinsed under running tap water.

Machine cleaning was considered adequate providing a detergent or enzymatic agent was used.

Results

All but one of the 140 Dutch general hospitals with facilities allowing general anaesthesia provided full details of their decontamination practices (response rate 99.3%). In 91 (65.5%) hospitals decontamination guidelines were present.

Fibrelight laryngoscope blades were used in 121 (87.1%) hospitals, conventional blades in 16 (11.5%) and in two (1.4%) hospitals both types were used. During decontamination of conventional blades the bulb was not removed in eight (44.4%) hospitals, it was removed in four (22.2%) and this was unclear in six (33.3%).

Manual decontamination—cleaning and subsequent disinfection by hand—was performed as standard practice in 109 (78%) of the 139 hospitals. However, in six of these hospitals (5.5%) decontamination by machines was performed as an exception. The reasons were: (1) 'infected patients' (three hospitals), (2) at the end of each day (two hospitals), and (3) once a week (one hospital).

Manual cleaning was performed in three (2.8%) hospitals by rinsing under running water only, in four (3.7%) by wiping only (without water), in two (1.7%) by brushing with a detergent solution (no running water), in 96 (88.1%) by brushing or wiping and rinsing under running water, and in four (3.7%) sometimes by brushing and rinsing under running water and sometimes only by rinsing under running water.

Detergents or enzymatic agents were used routinely in 93 (85.3%) hospitals, never used in 14 (12.8%), and sometimes used in two (1.8%). Disinfection was always carried out in 100 (91.7%) hospitals, never in five (4.6%) and occasionally in four (3.7%). The disinfectants used were: alcohols (ethanol 70%/isopropylalcohol 60%/others) in 86 (79.6%), a mixture of alcohol and chlorhexidine 0.5% in 21 (19.4%) and sodium dichloroisocyanurate 250 mg litre^{-1} in one (0.9%). Of the 107 alcohol based disinfectants, 7 (6.5%) were antiseptics.

The disinfectant was brought in contact with the blade by wiping with a soaked gauze in 80 (76.9%) hospitals, by fogging in two (1.9%), and by immersion in 22 (21.1%). The duration of immersion was unclear in nine hospitals and 10.9 min (2–30 min) (mean and range) in the others.

Decontamination using instrument-cleaning machines as the standard treatment was used in 30 (22%) of the 139 hospitals. In three of these hospitals the blades were subsequently sterilized; in two by autoclaving at 134°C (3.5 min) and in one by plasma sterilization (60 min, 93°C). In the other 27 (19.4%) hospitals, no subsequent sterilization procedure took place. In one of these hospitals, no detergent or enzymatic agent was used during decontamination. For these 27 hospitals the total duration of the washing cycle was ≥60 min in six (22%) hospitals, between 40 and 60 min in 17 (63%), between 20 and 40 min in two (7%) and unknown in two (7%). The maximum temperature reached was ≥90°C in 20 hospitals (74%), between 70 and 90°C in 3 (11%), less than 70°C in 3 (11%), and unknown in one (4%). The duration of maximum temperature was 12 min in one (4%) hospital, 10 min in four (15%), 9 min in two (7%), 5 min in two (7%), and unknown in 18 (67%).

Discussion

The results of this study show that there are substantial differences in the decontamination procedures in Dutch hospitals which compares with the situation in the UK.[2] However, more important is that the standards of the APIC, CDC and ASA, and the Dutch standard[7] (Table 1), are met in only the minority of these hospitals (maximal 19.4 and 26.6%, respectively) This represents a potentially harmful situation.

Manual decontamination

An important drawback of manual decontamination, practised in the majority of the hospitals in The Netherlands and the UK,[2] is that quality control is cumbersome, which has been recognized as a risk factor in the transmission of infectious agents.[1] To determine whether manual cleaning was being performed adequately, a standard is required. However, as there proved to be no standard, we developed our own, based on cleaning guidelines for endoscopes.[6 7] Using this modest standard, manual cleaning was inadequate in 25 (22.9%) of the 109 hospitals.

Manual disinfection results were even worse. None of the Dutch hospitals met the standards of the APIC, CDC or ASA. This was mainly because alcohols are no longer recognized to be high-level disinfectants.[6] Unfortunately,

Table 1 Cleaning and disinfection/sterilization guidelines of laryngoscope blades. *How to perform 'meticulous cleaning' is not well defined for laryngoscope blades. †High-level disinfection is a procedure that can be expected to destroy all micro-organisms, with the exception of high numbers of bacterial spores.[6] It can be achieved by high-level disinfectants or moist heat (70°C for 30 min).[5 6] ‡Ethanol 70% is not considered a high-level disinfectant.[5 6] When an antiseptic containing ethanol 70% was used, in this study this was considered equivalent with the use of ethanol 70%

Cleaning	
APIC/CDC/ASA/DWIC:	Always meticulous cleaning* before disinfection/sterilization
Disinfection	
APIC/CDC/DWIC:	High-level disinfection† or sterilization
DWIP:	Ethanol 70% immersion for 5 min‡
AMC:	Wiping with ethanol 70% gauze‡
APIC	Association of Professionals in Infection Control and Epidemiology[6]
CDC	Centers of Disease Control[5]
ASA	American Society of Anesthesiology
DWIP	Dutch Workingparty on Infection Prevention[7]
AMC:	Academic Medical Center; the hospital where this study was performed

the use of alternative high-level disinfectants (e.g. glutaraldehyde solutions) is complicated by Control of Substances Hazardous to Health (COSHH) regulations applicable throughout the European Union. However, even the Dutch standards—making the use of alcohol compulsory—were only met in 12 hospitals (11.0%). The majority failed to meet this standard as the method of application did not allow for the required contact time (5 min), because of the rapid evaporation of alcohol. Wiping the blade with alcohol, used in the majority of Dutch hospitals and also popular in other countries, has a questionable effect on the human immunodeficiency virus (HIV) and will not lead to the elimination of hepatitis B virus (HBV) or mycobacteria.[9 10] The same holds for fogging, which is not recommended by the CDC as it is potentially dangerous to the hospital worker.[5]

The concept of universal precautions, which dictates that decontamination procedures should be the same for each patient as each patient should be considered to be potentially infected with blood-borne pathogens,[11] was not followed in 7.2% of the Dutch hospitals. This is in contrast with the UK where 'only a few units practise universal precautions'.[2] Many studies—and logic—have proven the validity of this concept as patients infected with HIV, HBV or mycobacteria can not be distinguished from non-infected patients on clinical grounds.[1]

The use of antiseptics did not result in the judgement of inadequate disinfection although they are considered inappropriate for disinfection of medical equipment.[6] Much worse, however, was the use in 'special cases' of sodium dichloroisocyanurate in one hospital. This disinfectant is not approved in The Netherlands for use on medical equipment if used without subsequent mechanical cleaning and sterilization and the concentration used was 2.5 times the maximum concentration, representing a potential hazard.

Decontamination using machines

Although in three of the 30 hospitals routinely using instrument cleaning machines the blades were subsequently sterilized, leading to a clearly defined end result, the end result in the others was less certain; in many of them not all details of the disinfection process could be obtained. In addition, there is uncertainty about the temperature/time combinations needed for adequate disinfection, which according to the CDC, APIC and ASA is high-level disinfection. We were unable to find studies describing the lowest temperature/time combinations needed to eradicate the micro-organisms giving the highest infection rates as they are able to cross even intact mucous membranes; mycobacteria and viruses such as HBV.[6] It is questionable whether wet pasteurisation (30 min at 70°C), proposed by the APIC and CDC, will result in high-level disinfection, as infectivity of HBV in serum is not lost at 60°C for up to 4 h[12] and equipment should be boiled in water for at least 20 min before safe use can be guaranteed.[13] In addition, machines being able to provide these conditions must be validated to ensure the proper end result is reached.[14] The decontamination results in the 27 hospitals using instrument cleaning machines without subsequent sterilization were, according to the APIC, CDC and ASA guidelines, adequate in eight hospitals, probably adequate in 12, inadequate in three, and could not be determined in four hospitals.

Among the factors that have contributed to the great variety of decontamination procedures are the limited awareness of infection control procedures by many anaesthetic personnel[3 4 15–17] and the difficulty to establish a cause-effect relationship between anaesthetic practice and postoperative infection [16]. Only a few reports identified the laryngoscope as the most likely source of cross-infection.[18 19] which is in contrast to the other endoscopes. There seems to be no valid argument that this risk is any different for laryngoscopes, especially as blood is often encountered on the blade of the laryngoscope after use.[20 21]

Therefore, together with other authors,[16 17] we think that it is in the best interests of our patients to adhere to the infection control guidelines of the CDC, APIC and ASA where possible, until the safety of less conservative infection control practices has been established. Patients would rather support approved-guidelines than 'non compliant' practices,[17] which were recently compared in Newsweek with having unprotected sex.[22]

Our decontamination procedure was changed after this study; after buying laryngoscopes with the highest resistance to the damaging effect of sterilization,[23] all laryngoscopes are now mechanically cleaned and steam sterilized after use. Moreover, the Dutch guidelines are being changed and will soon be in accordance with the CDC, APIC and ASA guidelines.

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Appendix A

Questionnaire decontamination procedures laryngoscope blades

Name and telephone number of the hospital............/......

Type of laryngoscope:

brand: Penlon/Heine/Upsher/Medicon/Riester/Welch–Allyn/ other..

fibrelight/conventional/both

battery/accumulator/both

Do they have decontamination guidelines? yes/no

During decontamination of a conventional blade the bulb is:

not removed ○

removed ○

unclear whether it is removed ○
Decontamination is usually done:
by hand ○
by a machine ○
Are there exceptions and what are the reasons ....
Manual decontamination
cleaning
only rinsing with running water ○
only wiping (no water) ○
brushing with detergent solution (no running water) ○
wiping with a gauze and rinsing with running water ○
brushing and rinsing with running water ○
are detergents/enzymatic agents used? yes/no/sometimes
disinfection
disinfectant used?yes/no/sometimes
glutaraldehydes (e.g. Cidex™) ○
alcohol 70%/other ....○
other disinfectant ....○
contact with disinfectant by means of:
wiping with soaked gauze ○
fogging ○
immersion ○
duration of immersion.................min/unclear
Decontamination (/sterilization) by a machine
sterilization yes/no
by means of steam at 134°C/other ....
if no sterilization:
total duration of decontamination process.........min / ?
maximum temperature................................ °C / ?
duration of maximum temperature.................min / ?
agent(s) used:
detergent/enzymatic agent yes/no/unclear
others..

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BJA

LABORATORY INVESTIGATION

Mechanical and electrophysiological effects of thiopental on rat cardiac left ventricular papillary muscle

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Thiopental induces a negative inotropic effect on mammalian heart muscle, where it decreases Ca^{2+} current and Ca^{2+} release from the sarcoplasmic reticulum and reduces K^+ currents. We analysed the effects of thiopental on the mechanical and electrical activities of rat myocardium, which differ markedly from those of other mammals. The effects of thiopental on mechanical parameters and on the transmembrane resting (RP) and action (AP) potentials of rat left ventricular papillary muscle were investigated. These effects were also studied in the presence of atenolol, a β-blocking agent, and 4-aminopyridine (4-AP), a blocker of the transient outward K^+ current. Thiopental (3.8×10^{-6}, 3.8×10^{-5} and 1.1×10^{-4} M) induced a dose-dependent positive inotropic effect. This positive inotropic effect persisted in the presence of atenolol (1×10^{-6} M) but did not develop in the presence of 1 mM 4-AP; 4-AP had a positive inotropic effect but not in the presence of thiopental. Moreover, thiopental (3.8×10^{-5} M) lengthened the plateau and the slow repolarizing phase of the AP, while 1 mM 4-AP only prolonged the plateau duration. In rat myocardium, the positive inotropic effect of thiopental in part mimics that of 4-AP, and in part may be explained by the lengthening of the slow repolarizing phase of the AP.

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Thiopental, one of the drugs most commonly used for general anaesthesia, generally induces a depressive effect on the human cardiovascular system.[1] It has a direct negative inotropic effect on a wide variety of heart preparations, including dog,[2] rabbit,[3 4] guinea pig,[5 6] ferret[7] and human atrial tissue.[8] Thiopental decreases the Ca^{2+} current in dog[2] and guinea-pig[6] heart muscle. It also reduces the delayed outward K^+ current in guinea pig and rabbit[6 9] and frog heart muscle.[7] In rabbit heart muscle, thiopental reduces Ca^{2+} release from the sarcoplasmic reticulum (SR) and inhibits ryanodine-induced Ca^{2+} release from the SR[4] but does not alter Ca^{2+} uptake by the SR.[10] The direct negative inotropic effect of thiopental on ferret papillary muscle results from decreased intracellular Ca^{2+} availability and, at least in part, from inhibition of trans-sarcolemmal Ca^{2+} influx, despite a slight increase in myofibrillar sensitivity to Ca^{2+}.[7]

Numerous cellular processes regulating the homeostasis of contractile performance in rat myocardium differ from those observed in other species. Thus, in rat, Ca^{2+}-induced Ca^{2+}-release from the SR is more strongly developed than in other species.[11] In mammalian species, SR Ca^{2+}-ATPase activity is more prominent than Na^+/Ca^{2+} exchanger activity, but in the rat this dominance is much more marked (13-fold *vs* 2.5-fold).[12] Myosin ATPase activity and the percentage of the rapid V1 myosin isoform are higher in rat than in guinea-pig myocardium.[13] The plateau duration of the action potential (AP) in the rat is extremely short compared with that in the guinea pig[14] and most other mammals, including humans. Moreover, changes in AP duration and in the magnitude of contraction occurring during variations in heart rate are opposite in rat and in guinea pig.[14] Because of the special characteristics of rat heart muscle, as well as the various species-related effects of thiopental, the direction of the inotropic effect of thiopental on rat myocardium cannot be predicted. The aims of the present study were to test the effects of thiopental on

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contractile and electrical activities in rat cardiac left ventricular (LV) papillary muscle and to address the cellular mechanisms that might be involved in the positive inotropic effect induced by thiopental in rat myocardium.

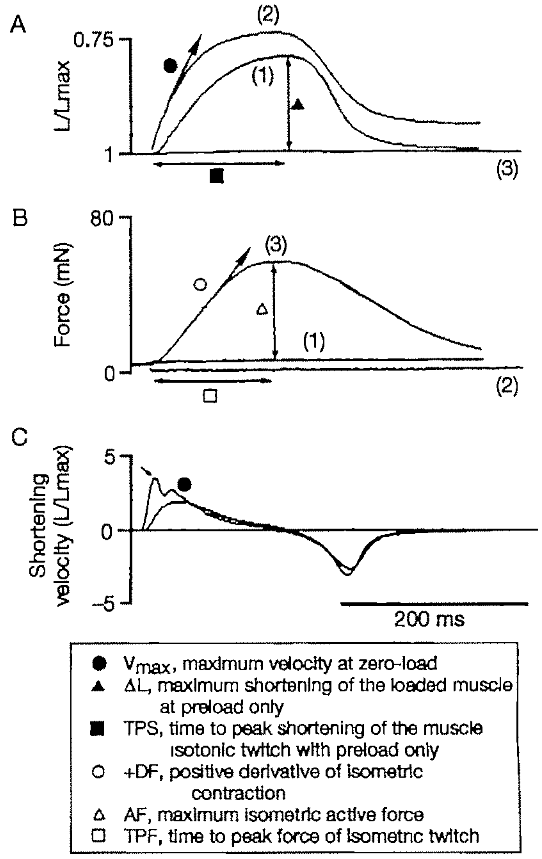

Fig 1 Mechanical parameters of contraction in LV rat papillary muscle. (A) muscle shortening length (L/L_{max}) plotted against time; (B) muscle force plotted against time; (C) muscle shortening velocity plotted against time. Twitch 1 was loaded at L_{max} with preload only. Twitch 2 was loaded with the same preload as that of twitch 1 and abruptly clamped to zero-load with critical damping just after the electrical stimulus. Twitch 3 was fully isometric. The following parameters of contraction were measured: V_{max} (maximum velocity at zero-load), ΔL (maximum shortening of the muscle at preload only, TPS (time to peak shortening of the isotonic twitch with preload only), +DF (positive derivative of isometric contraction), AF (maximum isometric active force), TPF (time to peak force of the isometric twitch). L (muscle length) and L_{max} (initial muscle length at peak active tension). The shortening length was expressed as the ratio L/L_{max}. In (C), the arrow represents the series element recoil; damping was adjusted to obtain a single oscillation.

Materials and methods

LV papillary muscles from adult Wistar rats (weighing 300–350 g) were used. Care of the animals conformed to the Helsinki Declaration, and the study was performed in accordance with the relevant French Ministry of Agriculture regulations.

Mechanical study

The heart was removed rapidly under ether anaesthesia. LV papillary muscles were carefully excised and suspended vertically in 40 ml of Krebs–Henseleit solution containing (in mM) 118 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.1 KH_2PO_4, 25 $NaHCO_3$, 2.5 $CaCl_2$, 4.5 glucose, bubbled with 95% oxygen/5% carbon dioxide (pH 7.4) and maintained at 29°C. The preparations were field-stimulated at 0.12 Hz by two platinum electrodes with rectangular wave pulses (5 ms duration) just above threshold. After a 1 h stabilization period at L_{max} (the initial muscle length at the apex of the length-active isometric tension curve), papillary muscles recovered their optimal performance. Suitable preparations were selected on the basis of the following criteria: (i) well individualized cylindrical shape, with cross-sectional area not exceeding 1.3 mm^2 and length at L_{max} of $\geqslant$3.5 mm, (ii) ratio of resting force to total isometric force <0.25 and (iii) ratio of maximum shortening and lengthening velocities <0.85 at load equal to preload at L_{max}. Adherent or bifid muscles were excluded from the study.

The electromagnetic lever system used to record mechanical data has been described elsewhere.[15] Signals of force and length were recorded and digitized; the sampling rate was 1 kHz. All analyses were performed on the basis of digital data without filtering. Mechanical parameters characterizing the contraction phase (inotropic state) were calculated from three twitches with different levels of preload and afterload (Figure 1). The first twitch was isotonic and was loaded with preload only. The second twitch was loaded with preload then abruptly clamped to zero-load immediately after the electrical stimulus, using the zero-load clamp technique. The muscle was released from preload to zero load with critical damping in order to slow the first rapid shortening overshoot resulting from the recoil of the series passive elastic component. This technique allows measurement of the maximum shortening velocity of the unloaded muscle, which is a good parameter of inotropy.[16] The third twitch was fully isometric.

The following contraction parameters (Figure 1) were studied: maximum unloaded shortening velocity (V_{max}, in L_{max} s^{-1}), determined by the zero-load clamp technique (twitch 2); maximum extent of muscle shortening of the twitch with preload only (ΔL, as a percentage of L_{max}) (twitch 1); peak isometric active force normalized per cross-sectional area (AF, in mN mm^{-2}); positive peak of the force derivative normalized per cross-sectional area of the fully isometric twitch (+DF, in mN s^{-1} mm^{-2}); time to peak force (TPF, in ms) of the isometric twitch (twitch 3); and time to peak shortening (TPS, in ms) of the isotonic twitch with preload only (twitch 1).

Control values of each mechanical parameter were first recorded using each muscle as its own control. Thiopental sodium (Specia) was added to the bath solution at three concentrations: 3.8×10^{-6} M (1 mg $litre^{-1}$) in group 1 (n=9); 3.8×10^{-5} M (10 mg $litre^{-1}$) in group 2 (n=13) and 1.1×10^{-4} M (30 mg $litre^{-1}$) in group 3 (n=9). Taking into account the protein binding of thiopental in blood, the concentration of

3.8×10^{-5} M corresponds to the free drug concentration, reached immediately after a bolus intravenous injection of 6 mg kg^{-1} thiopental in humans.[17] This concentration is higher than the concentration compatible with tracheal intubation in the rat.[18] In group 4 (n=15), the effect of 3.8×10^{-5} M thiopental was studied after adding 1×10^{-6} M atenolol (Zeneca Pharma), a selective β_1 adrenergic antagonist. In group 5 (n=9), 3.8×10^{-5} M thiopental was tested after adding 1 mM 4-aminopyridine (4-AP, Merck) to inhibit[19] the transient outward K^+ current (I_{to}). In group 6 (n=9), 1 mM 4-AP was applied after treatment with 3.8×10^{-5} M thiopental. Changes in mechanical parameters were studied 30 min after adding atenolol and 4-AP and 45 min after adding thiopental.

Electrophysiological study

LV papillary muscles were pinned to the bottom of the tissue chamber maintained at 29°C and superfused with Krebs–Henseleit solution at a rate of 15 ml min^{-1}. Muscles were electrically stimulated, at a frequency of 0.2 Hz, by means of square pulses (5 ms duration) delivered through bipolar earth-isolated platinum electrodes, using an opto-electric coupling device. Transmembrane resting (RP) and action (AP) potentials were recorded with conventional glass microelectrodes (resistance 25–30 MΩ; tip potential less than ±3 mV) filled with 3 M KCl and connected to a differential voltage follower via Ag–AgCl platinum black electrodes (20). Stimulated AP were recorded in Krebs–Henseleit control solution after a stabilization period of 30 min before and 10 min after the addition of thiopental (3.8×10^{-6} M) and (3.8×10^{-5} M), 1 mM 4-AP or both.

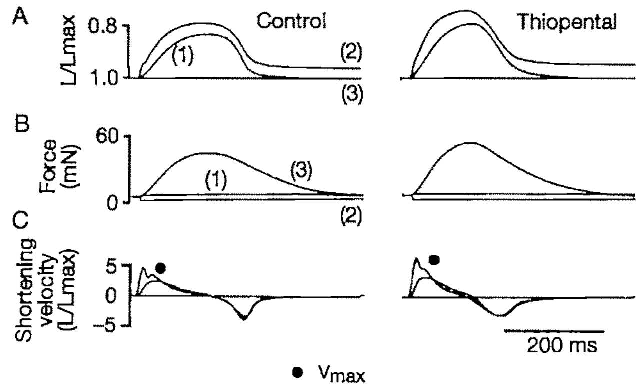

Fig 2 Effects of application of thiopental (3.8×10^{-5} M) for 45 min on mechanical parameters of contraction of rat papillary muscle recorded in Krebs–Henseleit solution (control); (a) muscle shortening length (L/L_{max}) plotted against time. (b) Muscle force plotted against time. (c) Shortening velocity plotted against time. Twitch 1 was loaded at L_{max} with preload only; twitch 2 was loaded with the same preload as twitch 1 and clamped to zero load just after the stimulus; twitch 3 was fully isometric at L_{max}.

The following AP parameters were measured: resting membrane potential (RP, in mV), overshoot (in mV), duration of the plateau (APD_0, in ms) measured at 0 mV, and duration of the slow repolarizing phase of the AP (APD_{10}, in ms) measured at +10 mV from the RP. In the figures, m corresponds to the number of impalements recorded from n muscles tested. Transmembrane potentials were displayed on a Nicolet 310 oscilloscope, digitized with a sampling rate of 1 kHz without filtering via a Labmaster acquisition card (DMA 100 OEM) driven by the software program Acquis1, linked to the mass storage of a personal computer.

Statistical analysis

Data are expressed as mean (SD). Comparisons with control values were made using Student's paired t test. Comparisons between groups were made using Student's t-test with the Bonferroni correction when appropriate. All P values were two-tailed; a P value of <0.05 was necessary to reject the null hypothesis.

Results

The addition of 3.8×10^{-5} M thiopental to the control solution induced a positive inotropic effect which reached a maximum steady-state value within 30 min, as shown in Figure 2. Table 1 summarizes the effect of increasing thiopental concentrations from 3.8×10^{-6} M to 1.1×10^{-4} M on the inotropic parameters. Thiopental significantly increased V_{max}, AF, +DF and ΔL, and shortened TPF and TPS. Only AF was unaffected by 1.1×10^{-4} M thiopental.

A significant increase in V_{max}, AF, +DF and ΔL occurred when thiopental (3.8×10^{-5} M) was applied to muscles

Table 1 Inotropic parameters of left ventricular rat papillary muscles measured in Krebs–Henseleit solution (control) before and 45 min after the addition of each thiopental concentration. Values are mean (SD). n, Number of muscles tested. Statistical significance of Student's t-test for each mean of thiopental group compared with mean of control group: *P<0.05, **P <0.001

Parameter	**Group 1 (n=9)**		**Group 2 (n=13)**		**Group 3 (n=9)**	
	Control	**Thiopental 3.8×10^{-6} M**	**Control**	**Thiopental 3.8×10^{-5} M**	**Control**	**Thiopental 1.1×10^{-4} M**
V_{max} (L_{max} s^{-1})	4.1 (0.9)	4.5 (0.9)**	4.4 (0.8)	5.1 (1.0)**	4.4 (1.0)	4.8 (0.9)*
ΔL (% L_{max})	20 (3)	21 (3)**	23 (4)	25 (3)**	23 (4)	25 (4)**
AF (mN mm^{-2})	55 (12)	58 (11)**	55 (13)	61 (13)**	56 (9)	58 (8)
+DF (mN s^{-1} mm^{-2})	638 (151)	693 (164)**	668 (165)	818 (183)*	716 (79)	797 (137)*
TPS (ms)	164 (8)	153 (6)**	160 (10)	152 (9)**	162 (10)	156 (7)*
TPF (ms)	162 (14)	149 (8)**	151 (12)	138 (15)**	152 (14)	136 (11)**

Table 2 Inotropic parameters of left ventricular rat papillary muscles in group 4 (n=15) measured in Krebs–Henseleit solution containing the blocker atenolol (1×10^{-6} M) applied 1 h before addition of 3.8×10^{-5} M thiopental (for 45 min). Values are mean (SD). n, Number of muscles tested. Student's t-test for paired data: $^{**}P<0.001$ for atenolol + thiopental compared with atenolol

Parameter	Atenolol	Atenolol + thiopental
$V_{\max}$ ($L_{\max}$ s^{-1})	4.7 (1.2)	5.0 (1.3)**
ΔL (% $L_{\max}$)	25 (6)	27 (6)**
AF (mN mm^{-2})	51 (14)	54 (17)**
+DF (mN s^{-1} mm^{-2})	608 (189)	665 (224)**

Table 3 Inotropic parameters of left ventricular rat papillary muscles in group 5 (n=9), measured in Krebs–Henseleit solution (control) before and after the addition of 1 mM 4-AP (for 30 min) then 3.8×10^{-5} M thiopental (for 45 min). Values are mean (SD). n, Number of muscles tested. Student's t-test for paired data with Bonferroni correction: $^{*}P<0.05$ and $^{**}P<0.001$ for 4-AP compared with control; $^{\dagger}P<0.05$ for 4-AP + thiopental compared with 4-AP

Parameter	Control	4-AP	4-AP + thiopental
$V_{\max}$ ($L_{\max}$ s^{-1})	4.2 (0.9)	4.7 (1.1)*	4.7 (0.8)
ΔL (% $L_{\max}$)	23 (4)	26 (4)**	26 (4)
AF (mN mm^{-2})	58 (21)	65 (22)**	59 (17)
+DF (mN s^{-1} mm^{-2})	734 (326)	885 (376)**	822 (308)†

Table 4 Inotropic parameters of left ventricular rat papillary muscles in group 6 (n=9), measured in Krebs–Henseleit solution (control) before and after addition of 3.8×10^{-5} M thiopental (for 45 min) then 1 mM 4-AP (for 30 min). Values are mean (SD). n, Number of muscles tested. Student's t-test for paired data with Bonferroni correction: $^{*}P<0.05$ and $^{**}P<0.001$ for thiopental compared with control

Parameter	Control	Thiopental	Thiopental + 4-AP
$V_{\max}$ ($L_{\max}$ s^{-1})	5.6 (0.9)	6.2 (1.2)**	5.9 (1.0)
ΔL (% $L_{\max}$)	24 (3)	26 (3)*	26 (3)
AF (mN mm^{-2})	63 (14)	71 (14)*	74 (15)
+DF (mN s^{-1} mm^{-2})	737 (172)	887 (195)**	927 (236)

previously treated with 1×10^{-6} M atenolol (Table 2). A positive inotropic effect was observed when 1 mM 4-AP was added to the Krebs–Henseleit solution. As shown in Table 3, 4-AP significantly increased $V_{\max}$, AF and +DF. Addition of thiopental (3.8×10^{-5} M) to a solution containing 4-AP failed to change the inotropic effect further, except for a slight (3%) but significant reduction in +DF (Table 3). Table 4 shows that addition of 4-AP to the solution containing 3.8×10^{-5} M thiopental had no effect on the inotropic parameters.

The addition of 3.8×10^{-5} M thiopental (Figure 3A and B) to the Krebs–Henseleit solution did not change the resting membrane potential or amplitude of the AP overshoot. In contrast, it lengthened the plateau (APD_0) and the slow final repolarization phase of AP (APD_{10}). The effects of 3.8×10^{-6} M and 3.8×10^{-5} M thiopental on the AP are summarized in Figure 3B; 3.8×10^{-6} M thiopental significantly lengthened APD_{10}, while 3.8×10^{-5} M thiopental lengthened both APD_0 and APD_{10}. The addition of 1 mM 4-AP to the control solution lengthened APD_0 but did not change RP or APD_{10} (Figure 4A). Further addition of thiopental (3.8×10^{-5} M) to the solution containing 4-AP (Figure 4A) markedly increased APD_{10} but did not change the other AP parameters. Figure 4B summarizes the effects of 4-AP alone on AP parameters and those established with further addition of thiopental (3.8×10^{-5} M) to the solution containing 4-AP.

Discussion

We examined the effects of thiopental at concentrations corresponding to plasma concentrations achieved during human[17] and rat[18] anaesthesia on the mechanical parameters and transmembrane potentials of rat cardiac papillary muscle. The main results were that (i) thiopental induced a positive inotropic effect and lengthened PA duration; (ii) it produced a positive inotropic effect on atenolol-pretreated muscles; and (iii) addition of thiopental to a solution containing 4-AP did not lead to any further increase in inotropy and addition of 4-AP to a solution containing thiopental did not increase inotropy. The positive inotropic response of rat heart muscle to thiopental reported in the present study differed markedly from that observed in other species[2–8] in which the drug causes a dose-dependent depression of contraction. In species other than rat, this negative inotropic effect may be due to an inhibitory effect of thiopental on the Ca^{2+} influx occurring via voltage-dependent Ca^{2+} channels, as suggested by the reduction of slow-channel-mediated action potentials in the dog,[2] the decline in the aequorin signal in ferret papillary muscle[7] and the reduction in the Ca^{2+} current in guinea-pig ventricular myocytes.[6] This negative inotropic response has also been attributed to an effect of thiopental on the SR. Thus, in rabbit heart muscle, thiopental reduces Ca^{2+} release from the SR and inhibits ryanodine-induced Ca^{2+} release from the SR.[4] To lead to a durable negative inotropic effect, however, the reduction in SR release must be accompanied by an alteration in uptake, causing a decrease in inotropy.[21] However, it has been shown that in the rabbit, thiopental does not alter Ca^{2+} uptake by the SR.[10] Moreover, some effects of thiopental are expected to generate a positive inotropic response, such as an increase in myofibrillar sensitivity to Ca^{2+} [7] and an increase in the duration of the AP. This lengthening of AP duration has been observed in dog papillary muscle,[2] in ventricular myocardium of rabbit[22] and frog[7 23] and in ventricular myocytes of guinea pig[6] and has been attributed to a reduction of K^+ conductances contributing to the repolarization of the cardiac AP. In frog atrial myocytes, thiopental depresses resting K^+ currents by attenuating the rectifying inward K^+ (I_{k1}) and delayed outward K^+ currents.[23] In guinea-pig and rabbit isolated ventricular myocytes, thiopental prolongs the repolarization of the AP, depresses the inward and outward

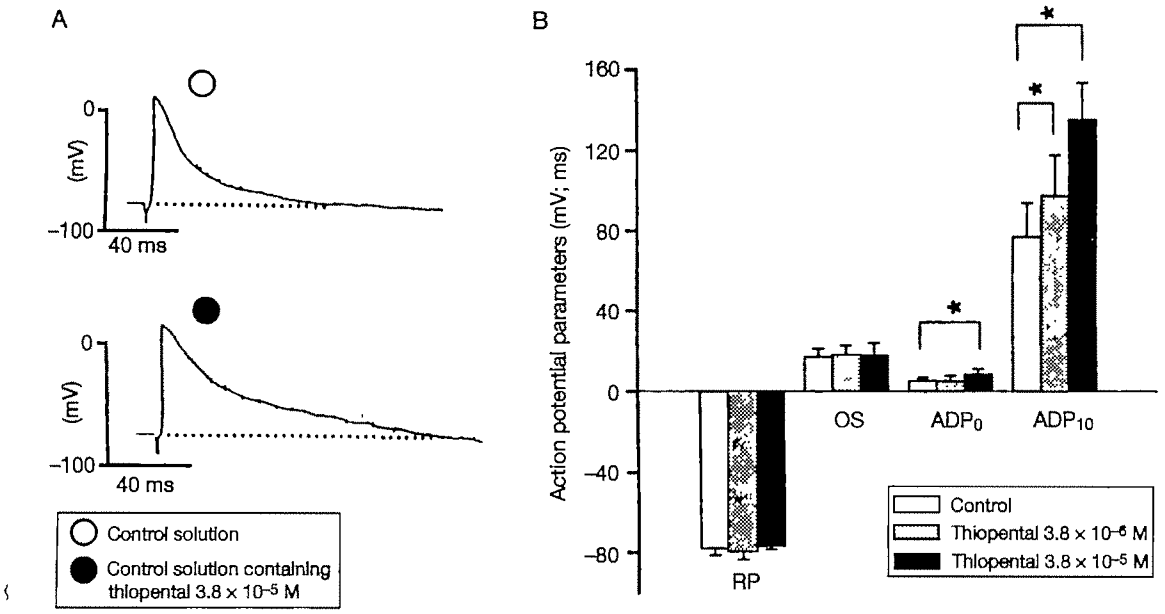

Fig 3 Effect of thiopental on the action potential (AP) of rat LV papillary muscle recorded in Krebs–Henseleit control solution at a frequency of 0.2 Hz, using intracellular microelectrodes. (A) AP traces recorded on the same papillary muscle. (B) Histogram showing the effect of 3.8×10^{-6} M and 3.8×10^{-5} M thiopental on the AP parameters. Mean±SD of m impalements recorded from n muscles. control: m=20, n=8; thiopental 3.8×10^{-6} M: m=12, n=4; thiopental 3.8×10^{-5} M: m=16, n=6. Student's t-test for paired data:$^*P<0.05$. RP, resting membrane potential; OS, overshoot; APD_0, duration of the plateau measured at 0 mV; APD_{10}, duration of the slow repolarizing phase of the AP measured at a membrane potential +10 mV higher than RP.

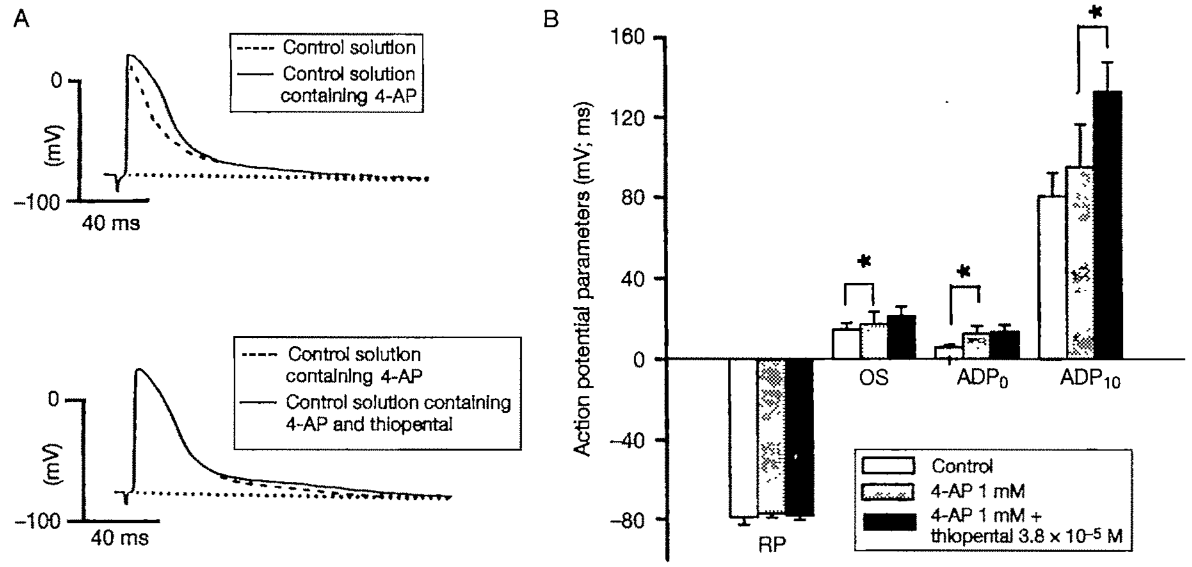

Fig 4 Effect of 1 mM 4-aminopyridine (4-AP) and 3.8×10^{-5} M thiopental on the action potential (AP) of rat papillary muscle recorded in Krebs–Henseleit solution, at a frequency of 0.2 Hz, using intracellular microelectrodes. (A) Top: dashed line, control solution; solid line, 4-AP; bottom: dashed line, 4-AP; solid line, control solution containing 4-AP and thiopental. (B) Histogram showing the effect of successive addition of 4-AP and thiopental in the control solution (empty bar) on the AP parameters. Mean±SD of m impalements recorded from n muscles. Control: m=20, n=8; 4-AP: m=31, n=4; 4-AP + thiopental 3.8×10^{-5} M: m=30, n=4. Student's t-test for paired data: $^*P<0.05$. RP, resting membrane potential; OS, overshoot; APD_0, duration of the plateau measured at 0 mV; APD_{10}, duration of the slow repolarizing phase of the AP measured at a membrane potential +10 mV higher than RP.

components of the inward rectifier K^+ current and inhibits the delayed rectifier K^+ current.[9] Thiopental has also been reported to reduce I_{k1} in rat and human ventricular myocytes.[24] It is generally accepted that lengthening of the cardiac AP increases the availability of intracellular Ca^{2+} and produces a positive inotropic effect.[25] Moreover, thiopental induces a slight increase in myofibrillar sensitivity to Ca^{2+} which may help produce a positive inotropic effect on myocardium.[7] The ability of thiopental to prolong the AP conflicts with its negative inotropic effect induced in most species. The direction of change in inotropy after thiopental treatment in cardiac muscle is partly determined by the overall resultant of the different and opposed effects of thiopental on (i) transsarcolemmal Ca^{2+} and K^+ currents, (ii) Ca^{2+} movement through the SR membrane and (iii) myofibrillar sensitivity to Ca^{2+}. In most species, this resultant effect is negative,[2–8] except in our study where it was shown to be positive in the rat. However, this effect is certainly dose dependent and it has been shown that the percentage of cell shortening in rat ventricular myocytes is significantly altered[26] at a thiopental concentration of $>1\times10^{-4}$ M. The observation in our study that the inotropic effect of thiopental was still present when β-receptors were blocked by atenolol suggested that this effect of thiopental on the inotropy of rat papillary muscle cannot be attributed to an agonist effect of the anaesthetic on β adrenoceptors, but involves a mechanism different from activation of the cAMP cascade.

Rat cardiac AP consists of a spike induced by the fast inward Na^+ current, followed by a short plateau generated by the inward Ca^{2+} current, which is modulated by the transient outward K^+ current (I_{to}), and a slow repolarization phase thought to be due to the development of the delayed outward K^+ current and the electrogenicity (3 Na^+/1 Ca^{2+}) of the Na^+/Ca^{2+} exchanger.[14 16 27] The importance of I_{to}[28] in determining early repolarization during the plateau has been shown in normal[29] and pathological[30] mammalian cardiac muscles. Inhibition of I_{to} by 4-AP in rat heart muscle increases the duration of the AP plateau.[19]

In our study, the lengthening of the plateau induced by thiopental suggests that the anaesthetic exerted a 4-AP-like effect. Lengthening of the AP of rat cardiac ventricular myocytes, after application of a control solution containing 4-AP, leads to a more sustained Ca^{2+} current associated with an increased contractile response.[25] 4-AP had a marked positive inotropic effect on rat left ventricular papillary muscle. Thus, the extended plateau induced by thiopental which occurred in a range of membrane potentials within which a large proportion of Ca^{2+} channels remains activated, may partly account for the increase in contractile force.

Thiopental also lengthened the slow repolarizing phase of the AP. This lengthening occurred in the presence or absence of 4-AP and may be a result of a decrease in both the delayed outward K^+ current and I_{K1}.[9 23] Lengthening of AP duration has been associated with an increase of inotropy because greater Ca^{2+} influx is expected during this period. Given that, in rat myocardium, Ca^{2+}-induced Ca^{2+} release from the SR is highly sensitive to Ca^{2+} influx into the cells,[31] greater Ca^{2+} influx during the AP may contribute to increased Ca^{2+} release from the SR and thus to a positive inotropic effect. Such a mechanism is suggested to explain the positive inotropic effect of an α1-adrenergic agent[32] and of the immunosuppressant agent FK 506.[33] However, to maintain a positive effect on the systolic Ca^{2+} transient, a drug may also modify processes other than Ca^{2+}-induced Ca^{2+} release.[21] For example, in the case of FK 506 it has been suggested that the sustained positive inotropic effect could be due to inhibition of the Na^+/Ca^{2+} exchange, resulting in an increase in Ca^{2+} availability for SR uptake. In the case of thiopental, further studies are necessary to investigate such a mechanism.

One of the limitations of our study is the use of a low stimulation frequency. In the rat, a low stimulation frequency induces an increase in inotropy because a prolonged diastole leads to an increase in SR Ca^{2+} uptake. Each contraction takes place after an 8 s diastolic pause, allowing a return to baseline diastolic Ca^{2+} level, thus, a drug-induced anomaly of this uptake can be hidden. However, most mechanical studies use such a low frequency to avoid the many rhythm anomalies induced by high frequencies. Moreover, it has been shown that thiopental does not alter SR uptake, at least in the rabbit.[10]

In conclusion, this study shows that thiopental increases inotropy in rat cardiac papillary muscle. This positive inotropic effect can be linked to the lengthening of both the plateau and the slow repolarizing phase of the AP. This leads to an increase in the Ca^{2+} influx into the cardiac cells, which improves mechanical performance.

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BJA

REVIEW ARTICLE

Lazaroids: efficacy and mechanism of action of the 21-aminosteroids in neuroprotection

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Methylprednisolone, administered in high doses (30 mg kg^{-1}), reduces neurological damage and promotes functional recovery following central nervous system injury in animal studies,[27] and is an established therapy to improve neurological recovery after spinal cord injury in humans.[10] At these doses, methylprednisolone inhibits lipid peroxidation of neuronal, glial and vascular membranes caused by oxygen free radicals,[3 4 12 13] a process implicated in the pathophysiology of secondary central nervous system (CNS) injury.[4] The neuroprotective effects are independent of its glucocorticoid receptor actions. The realization that the efficacy of methylprednisolone in reducing secondary injury was separate from its hormonal activity stimulated the development of a group of steroid analogues, the lazaroids (21-aminosteroids), that specifically inhibited lipid peroxidation without glucocorticoid or mineralocorticoid activity, thereby avoiding the complications of corticosteroid therapy.

Lipid peroxidation and cerebral injury

During ischaemia and reperfusion injury of the CNS, mitochondrial dysfunction produces oxygen free radicals that cause lipid peroxidation of cell membranes resulting in membrane disintegration and increased microvascular permeability. Lipid peroxidation is catalysed by free iron derived from haemoglobin released from extravasated red blood cells. Disruption of neuronal, glial and vascular membranes inhibits Na^+/K^+ ATPase and Ca^{2+}ATPase.[68] This increases cellular influx of calcium ions which activate phospholipase A_2 resulting in a release of arachidonic acid. The production of metabolites such as platelet-activating factor, prostaglandin E_2 andleukotriene B_4 enhances inflammation. The oxygen free radicals and leukotriene B_4 activate neutrophils in the damaged tissues. Lipid peroxidation of cell membranes enhances further generation of oxygen free radicals and activation of phospholipase A_2. Ultimately, cell death with leakage of cytoplasmic components and arachidonic acid into the extracellular environment occurs. Lipid peroxidation of vascular endothelium also causes the increased permeability of the blood–brain barrier associated with trauma and ischaemic injury, and may produce prolonged cerebral vasospasm after subarachnoid haemorrhage.

During ischaemia, superoxide anions ($\cdot O_2$) are produced by enzyme–substrate reactions in the mitochondria, especially during reperfusion. Other sources of free radicals include the oxidation of monoamine neurotransmitters by monoamine oxidase and activated neutrophils that invade the CNS after trauma and hypoxaemia. Superoxide dismutase breaks the superoxide anion down to hydrogen peroxide (H_2O_2), which is reduced to a highly reactive hydroxyl free radical ($\cdot OH$). This reduction reaction is catalysed by ferrous ions. These free radicals ($\cdot OH$, $\cdot O_2$) are scavenged normally by membrane-bound endogenous antioxidants, especially vitamin E. In primary cerebral injury, the increased formation of these free radicals overwhelms the endogenous defence mechanisms.

Lipid peroxidation, initiated by a chain reaction involving oxygen free radicals, produces lipid peroxyl radical that attacks unsaturated fatty acids of membrane phospholipids, forming unstable, highly reactive lipid hydroperoxide radicals. Alpha-tocopherol, an important endogenous inhibitor, limits lipid peroxidation by scavenging lipid peroxyl radicals, thus preventing the lipid radical chain reaction from occurring.

The CNS is particularly susceptible to lipid peroxidation because its membrane lipids are rich in polyunsaturated fatty acids that possess reactive hydrogen. The brain has a relatively weak antioxidant capacity relative to other organs. In addition it is rich in intracellular iron which is released during injury, and the cerebrospinal fluid (CSF) has less transferrin than plasma to bind the iron.

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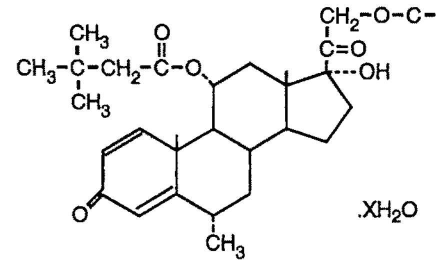

Fig 1 U-72099E, a non-glucocorticoid steroid.

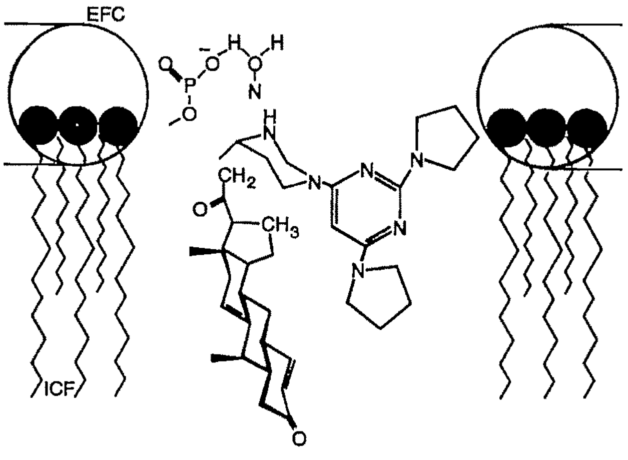

Fig 2 Membrane stabilizing effects of lazaroids. Tirilazad is incorporated into the lipid bilayer and the interaction between the piperazine nitrogen of tirilazad and the phosphate groups of the lipid membrane stabilizes the membrane by restricting lipid peroxyl radical interaction. EFC, extracellular fluid compartment; ICF, intracellular fluid.

History of lazaroids

Early analogues of methylprednisolone that lacked glucocorticoid activity due to the substitution of the 11-β-hydroxy group (e.g. U-72099E; Fig. 1) were developed, but these inhibited lipid peroxidation weakly. The lazaroids are unique compounds possessing the membrane-stabilizing effects of the glucocorticoids without the receptor-dependent side effects. One of these compounds, tirilazad mesylate (U-74006F) has been selected for clinical development as a parenteral neuroprotective agent.

Mechanism of action

The lazaroids exert their anti-lipid peroxidation action through two mechanisms, free radical scavenging and membrane stabilization. Early animal studies of traumatic and ischaemic injury[31 35 70] suggest that the lazaroids inhibit membrane lipid peroxidation by scavenging peroxyl radicals, a mechanism similar to that of vitamin E.[14] In experimental head injury models, tirilazad decreased hydroxyl radical production in the brain of mice produced by concussive head injury, and in gerbils with bilateral carotid occlusion indicating that it may also scavenge hydroxyl radicals.[1 5 34]

The lazaroids also have potent cell membrane-stabilizing effects. They have a high affinity for the lipid bilayer and are incorporated into the lipid bilayer.[38] The positively charged piperazine nitrogen in tirilazad interacts with the negatively charged phosphate-containing head groups of the membrane lipids[29] (Fig. 2). The localization of the bulky 21-amino moiety towards the surface compresses the membrane phospholipid head groups. This membrane-stabilizing action restricts the movement of lipid peroxyl radicals within the membrane so that their interaction with neighbouring fatty acids is reduced, thus inhibiting lipid peroxidation.

Pharmacodynamics

Although tirilazad is lipophilic, it penetrates the blood—brain barrier poorly. It is highly concentrated in the vascular endothelial cell membrane,[67] and this indicates an endothelial site of action. Tirilazad prevents increases in blood–brain barrier permeability in acute trauma[32] and subarachnoid haemorrhage[87] in animal models. This is mediated by preservation of endothelial function via reduction of oxygen radical damage, and maintenance of production and function of endothelial nitric oxide.[18] In cerebral injury, a loss of endothelial function contributes to the loss of autoregulation, microvascular hypoperfusion and vasospasm. However, direct neuronal protection by tirilazad cannot be ruled out because enhanced penetration into brain parenchyma, caused by increased blood–brain barrier permeability,[34] has been observed after trauma.

Pharmacokinetics

The pharmacokinetics of tirilazad has been studied after single and multiple doses. Tirilazad is extensively distributed in body tissues. It is 99% protein bound with a volume of distribution of ~3.33 litres kg^{-1}.[20] With multiple doses at 2 mg kg^{-1} day^{-1} and above, its terminal half-life is ~35 h, so that a steady state is achieved after 5 days of dosing. The hepatic clearance of tirilazad is dependent on hepatic blood flow suggesting that it has a medium to high hepatic extraction ratio.[21] Tirilazad is metabolized in the liver to several inactive oxidative products and a reduced metabolite, U-89678, which is active.[80] The clearance of tirilazad and its active metabolite (U-89678) is slightly greater in women,[42] due to gender differences in either hepatic blood flow, or metabolism of the steroid moiety of the molecule.[52 81] The elimination of tirilazad is increased by enzyme-inducing anticonvulsants such as phenytoin.[19] Only 12% of the dose may be recovered in the urine and most of it is in the faeces.[76]

Side effects

Extensive animal and human studies of single and multiple doses of tirilazad (up to 6 mg kg^{-1} day^{-1} for 5 days) demonstrated minimal changes in heart rate, blood pressure or cardiac rhythm. It does not significantly affect plasma glucose, cortisol or adrenocorticotrophin concentrations and temperature regulation.[20 21] A transient rise in serum alanine transaminase concentrations in human subjects receiving 6 mg kg^{-1} day^{-1} for 5 days has been reported.[21] The most common side effect is pain at the injection site caused by the vehicle (0.02 M citric acid monohydrate, 0.0032 M sodium citrate dihydrate, 0.077 M NaCl, pH 3).[21]

Central nervous system trauma

Free radical production and lipid peroxidation are early biochemical events in the pathogenesis of traumatic brain injury. In CNS trauma, tissue haemorrhage initiates free radical formation, and iron compounds released from blood cells catalyse the formation of hydroxyl radicals and stimulate membrane lipid peroxidation. Free radicals are known to increase blood–brain barrier permeability and lazaroids may protect the blood–brain barrier by reducing hydroxyl radicals or protect the microvascular endothelium from lipid peroxidation.

Preventing and reducing secondary brain injury have been the main areas of CNS trauma research. In head injury, the therapeutic efficacy of the lazaroids has been focussed on their role on membrane damage resulting from free radical reactions and the disruption in cellular ionic homeostasis, with less attention to other pathophysiological mechanisms such as release of excitotoxic amino acids.

Experimental data

Head injury

Studies on functional outcome in animal models of head injury demonstrated beneficial effects of tirilazad. Mice receiving doses of tirilazad ranging from 0.003 to 30 mg kg^{-1} at 5 min after a standard head injury were significantly better neurologically after 1 h compared with controls. Mice treated with tirilazad 1 mg kg^{-1} at 5 min and 1 h post-injury had a survival of 78.6% at 1 week compared with 27.3% in the control group.[36] Male Sprague–Dawley rats subjected to brain injury produced by fluid percussion over the left parietal cortex had no mortality at 48 h post-injury when tirilazad 3 mg kg^{-1} was administered at 15 min and 3 h post-injury, compared with a mortality of 28% in control groups.[57] However, in another study, rats that were hypoxic for 45 min after a standard head injury received doses of tirilazad varying from 1 to 30 mg kg^{-1} at 3 min and 3 h after injury. Only the group receiving tirilazad at 10 mg kg^{-1} showed significantly improved motor scores measured at 24 h after injury.[69]

Further studies demonstrated the beneficial effects of tirilazad on cerebral metabolic function, blood–brain barrier permeability and cerebral oedema in animals. Tirilazad 1 mg kg^{-1} administered to female mongrel cats 30 min after a severe unilateral cerebral contusion, with a further dose of 0.5 mg kg^{-1} 2.5 h after injury, improved the metabolic state in the neighbouring non-oedematous white matter (indicated by the glucose, lactate and glycogen concentrations).[16] Oedema and the amount of metabolites in contused tissue were similar in vehicle-treated and drug-treated groups.

In a head injury model in rats, tirilazad diminished the post-traumatic increase in blood–brain barrier permeability. Tirilazad 10 mg kg^{-1} administered 5 min post-injury reduced parenchymal extravasation of protein-bound Evans blue at 30 min by 52%.[32] Using autoradiographic techniques, tirilazad 10 mg kg^{-1} has been shown to reduce microvascular changes in permeability when administered 5 min after head injury in rats.[56] Another 21-aminosteroid, U-74389F, administered over a range of doses pre- and post-injury, reduced brain swelling in Sprague–Dawley rats exposed to a cryogenic brain injury.[72]

Spinal cord injury

Animal studies[17 40 41] demonstrated that tirilazad improved functional recovery and blood flow in the white matter of the spinal cord during injury. Female mongrel cats receiving tirilazad 0.16–160 mg kg^{-1} 48 h^{-1} followed by an infusion for 42 h after a spinal cord injury had improved functional recovery 3 weeks post-injury compared with the control group.[2] Tirilazad (single dose of 10 mg kg^{-1}) prevented the fall in blood flow in spinal cord white matter after a spinal cord injury in cats. Normal blood flow in the white matter of the spinal cord was reported 4 h post-injury, compared with a 63% decreased flow in the control groups.[26] However, tirilazad 3 mg kg^{-1} administered 30 min before spinal cord injury in rats, and 1.5 mg kg^{-1} every hour after injury failed to attenuate the rise in plasma lactate and glutamate concentrations (markers of ischaemia). Most significantly, the lowering of lactate and arginine concentrations early after trauma observed with methylprednisolone pre-treatment was absent after pre-treatment with tirilazad.[17]

Clinical data

In a multi-centre trial evaluating tirilazad in patients with head injury,[54] 1120 patients received at least one dose of either tirilazad or placebo. Eighty-five percent of the patients had severe and 15% moderate head injury (Glasgow Coma Score 4–8). After 6 months, there was no difference in functional recovery or mortality. Subgroup analysis suggested an improvement in mortality in males with severe head injury and accompanying traumatic subarachnoid haemorrhage who received tirilazad. However, there were differences between the two groups with respect to prognostic variables such as pre-treatment hypotension, pre-treatment hypoxaemia and epidural haematoma.[54]

In a randomized, double-blind multi-centre trial[11] investigating the efficacy of tirilazad in spinal cord injury, 499 patients with spinal cord injury diagnosed within 8 h of injury were randomized into three groups. All patients received an initial bolus of methylprednisolone 30 mg kg^{-1}. The first group received standard therapy of a methylprednisolone infusion of 5.4 mg kg^{-1} h^{-1} for 24 h. The second group received a similar infusion for 48 h. The tirilazad group received tirilazad (2.5 mg kg^{-1} boluses) every 6 h for 48 h. Patients who received tirilazad had equivalent recovery rates to those patients receiving methylprednisolone for 24 h with respect to motor function changes and functional independence at 6 weeks and 6 months. However, those patients who received therapy within 3–8 h after injury had a significantly better outcome at 6 months (P=0.01) with a regimen of methylprednisolone for 48 h, compared with a regimen of methylprednisolone for 24 h or tirilazad for 48 h. Although the group receiving tirilazad for 48 h had fewer complications, this was not clinically or statistically significant. It was postulated that the reduced efficacy of tirilazad compared with methylprednisolone might be due to a suboptimal dosage. Further analysis showed that the patients randomized to receive tirilazad had significantly worse motor scores prior to treatment compared with the other groups.[11] In conclusion, the study did not justify the use of tirilazad clinically in spinal injuries, and further studies with higher doses and longer regimes are required.

Central nervous system ischaemia

There is considerable evidence of lipid peroxidation in cerebral ischaemia. During and after an ischaemic insult, cellular calcium influx influences the extent of neuronal injury. In addition, post-ischaemic production of lactate in the damaged tissues causes mitochondrial dysfunction resulting in the generation of toxic free radicals. Animal studies have indicated that tirilazad may attenuate cell damage with transient or permanent focal ischaemia associated with thromboembolism, and transient global ischaemia in cardiopulmonary arrest.

Experimental data

Focal transient ischaemia

In a model of temporary hemispheric cerebral ischaemia in Mongolian gerbils, tirilazad 10 mg kg^{-1}, when administered before and after a 3-h unilateral carotid artery occlusion, significantly improved the 24 and 48 h survival, and preserved neurones in the hippocampus and lateral cortex.[30] The neuroprotective mechanisms of tirilazad attenuated post-ischaemic depletion of vitamin E,[70] improved post-ischaemic recovery in extracellular calcium levels,[31] preserved levels of the antioxidant ascorbic acid,[68] and diminished hydroxyl radical production during reperfusion.[5] Tirilazad also decreased the infiltration of neutrophils into the reperfused hemisphere[61] associated with reduced brain concentrations of the leukotrienes C_4 and B_4 post-ischaemia.[6] In cats, tirilazad, administered as a series of boluses after middle cerebral artery occlusion for 1 h, reduced infarct size[71 73] but had no effect when the arterial occlusion was prolonged to 90 min.[22 77]

In focal ischaemia, tirilazad 10 mg kg^{-1} administered to Wistar rats 2 h before middle cerebral artery occlusion (for a 2-h period) reduced post-ischaemia infarct volume at 24 h by 67% compared with controls.[83] In a similar study with male Sprague–Dawley rats, tirilazad administered before and after a 90-min occlusion of the middle cerebral artery reduced infarct size at 24 h by 48%, compared with controls.[71] In Cynomolgous monkeys subjected to 3 h middle cerebral artery occlusion, the administration of tirilazad 3 mg kg^{-1} 10 min before reperfusion attenuated post-ischaemia brain oedema.[9]

Permanent focal ischaemia

As lazaroids act primarily by preventing damage caused by free radicals generated during cerebral reperfusion after a period of ischaemia, it is suggested that lazaroids are most effective in transient ischaemia and less effective in permanent ischaemia. However, there are good experimental data to support their role in therapy for permanent focal ischaemia.[62]

A number of studies investigating the effects of single or multiple doses of tirilazad 1–3 mg kg^{-1} administered after permanent unilateral middle cerebral artery occlusion in Sprague–Dawley rats have reported a reduction in infarct size and oedema formation.[8 53 85] A reduction in cerebral oedema, Na^+ accumulation and K^+ loss mainly limited to areas of the cortex adjacent to the infarct site has been demonstrated.[85] In a similar rat model of permanent focal ischaemia, tirilazad significantly reduced the amount of lipid peroxidation products and free arachidonic acid in the infarcted hemisphere. The extent of ischaemic damage is significantly correlated with the concentration of these products.[78] However, two studies investigating tirilazad 10 mg kg^{-1} failed to show a protective effect in models of permanent focal ischaemia in the spontaneously hypertensive rats[84] and hyperglycaemic cats.[59]

Tirilazad has been shown to be efficacious in two rabbit models of thromboembolic stroke. Pre- and post-treatment with tirilazad of rabbits subjected to an internal carotid arterial injection of a 3.5-cm embolus significantly reduced infarct size in the affected hemisphere.[82] In the second study, microspheres were injected into the internal carotid artery until a functional deficit was produced. In this study, pre-treatment but not post-treatment with tirilazad 3 mg kg^{-1} doubled the number of microspheres needed to produce a 50% functional deficit.[15]

Global cerebral ischaemia

The efficacy of tirilazad in cardiac arrest and resuscitation has been examined in animal models of global cerebral ischaemia and reperfusion. In a rat model (employing transient bilateral carotid occlusion with hypotension for 10 min), tirilazad, in doses ranging from 0.3 to 10 mg kg^{-1} given before and after the ischaemic injury, abolished post-ischaemic increases in nitric oxide synthase and cyclic guanosine monophosphate concentrations in brain homogenates[18] and reduced cortical neuronal loss.[51] Another study showed that when tirilazad was given before or after ischaemia, there was a faster recovery of high-energy phosphates during early reperfusion.[37] In this model, however, selectively vulnerable neurones in the hippocampus and striatum were not protected by tirilazad.[8 39 51] However, the production of toxic hydroxyl radicals in the rat hippocampus during ischaemia and reperfusion is attenuated by lazaroids.[86] When the duration of global ischaemia was increased to 30 min, the protective effect of tirilazad was lost.[45 64]

Other animal models of global ischaemia have also shown a generally positive outcome with tirilazad. In a model of incomplete cerebral ischaemia in anaesthetized dogs,[55] cerebral perfusion pressure was reduced to 12 mm Hg for 30 min with an intraventricular fluid infusion. Tirilazad 1 mg kg^{-1}, administered pre- and post-ischaemia, augmented recovery of inorganic phosphate and somatosensory-evoked potentials with resolution of intracellular acidosis during reperfusion and decreased cerebral oedema.[55] Tirilazad 0.25–2.5 mg kg^{-1} administered only in the reperfusion stage significantly improved recovery in cerebral oxygenconsumption, cerebral blood flow, ATP and the resolution of intracellular acidosis in this dog model.[47]

When complete cerebral ischaemia was produced for 12 min in anaesthetized dogs by raising ICP above systemic arterial pressure with ventricular fluid infusion, functional recovery at 48 h markedly improved with tirilazad 1.5 mg kg^{-1} given before and after ischaemia.[63] However, tirilazad had no effect on the recovery of intracellular pH, oxygen consumption, somatosensory-evoked potentials and cerebral blood flow during a 3-h reperfusion phase.[23]

Clinical data

Clinical studies looking at the cerebroprotective efficacy of tirilazad in cerebral ischaemia have been disappointing. A large prospective double-blind, randomized trial in which 660 patients received either vehicle (control) or tirilazad 6 mg kg^{-1} day^{-1} for 3 days (with the first dose given within 6 h of onset of acute stroke) evaluated the outcome at 3 months after stroke.[65] Tirilazad had no positive effect on the Glasgow Outcome Scale and the Barthel index of activities of daily living. The odds ratio of a favourable outcome in favour of tirilazad was 0.87 (95% confidence interval, 0.6–1.25) for both the Glasgow Outcome Scale and the Barthel Index. This lack of benefit might be due to inadequate dosage. A second clinical study[66] using higher doses in both men (12.5 mg kg^{-1} on day 1 and then 10 mg kg^{-1} day^{-1} for 2 days) and women (15 mg kg^{-1} on day 1 then 12.5 mg kg^{-1} day^{-1} for 2 days) was conducted. One hundred and twenty-six patients were enrolled and matched for baseline characteristics in each treatment group. Tirilazad was associated with an absolute reduction in mortality of 14% in both sexes. However, the numbers in this study were small and the differences were not statistically significant.[66] No clinical studies evaluating the role of tirilazad in cerebroprotection during cardiopulmonary resuscitation have been conducted as yet.

It is important to emphasize that the mediators of secondary damage during ischaemia and reperfusion include release of excitotoxic amino acids, free radicals and microcirculatory disturbances. Free radical damage of cell membranes is only one pathophysiological mechanism of many during reperfusion. A combination of several therapeutic modalities such as arterial pressure stabilization, glutamate antagonists and correction of tissue acidosis may significantly improve outcome.

Subarachnoid haemorrhage

Following subarachnoid haemorrhages, secondary cerebral ischaemia occurs as a result of microvascular hypoperfusion associated with a decrease in blood–brain barrier permeability, vasogenic oedema, increased intracranial pressure and delayed vasospasm. Lipid peroxidation in the arterial walls after SAH plays an important role in genesis of vasospasm.

Experimental data

Effect on cerebral microvascular hypoperfusion

In a model of subarachnoid haemorrhage produced by injecting autologous blood into the cisternae magna of anaesthetized cats, tirilazad 0.1 mg kg^{-1} and 1 mg kg^{-1} administered 30 min after the insult attenuated significantly the fall in blood flow in the caudate nucleus and diminished the increase in intracranial pressure. It also attenuated the concomitant fall in mean arterial pressure and cerebral perfusion pressure.[33]

Effect on blood–brain barrier permeability

Endothelial cell cultures undergo marked increase in permeability when exposed to haemolysed red cells. This was significantly attenuated by pre-treatment with tirilazad,[48] indicating that free radical generation causing lipid peroxidation was a critical mechanism responsible for the increased permeability. Two studies[72 87] investigating the effect of pre- and post-treatment with tirilazad on blood—brain barrier permeability after the injection of autologous blood into the subarachnoid spaces of rats showed that tirilazad significantly attenuated the increase in permeability to albumin compared with control. Tirilazad has been shown to attenuate increased blood–brain barrier permeability associated with subarachnoid injection of arachidonic acid and $FeCl_2$.[87]

Effects on delayed cerebral vasospasm

Tirilazad is potentially beneficial in the management of delayed onset vasospasm as its action is primarily at the vascular endothelium. Lipid peroxidation plays a substantial role in cerebral vasospasm,[7] which normally occurs several days after the initial subarachnoid bleed. Consequently, therapy can be started before its onset.

In a canine model of subarachnoid haemorrhage, tirilazad 0.5 mg kg^{-1} administered every 8 h for 6 days, either as an infusion or as boluses significantly attenuated intraluminal narrowing of the basilar artery compared with control.[57] Three studies[43 44 75] using the Cynomolgous monkey model of subarachnoid haemorrhage have shown that tirilazad 0.3–3 mg kg^{-1} administered every 8 h for 6 days post-haemorrhage, significantly reduced middle cerebral artery vasospasm. However, tirilazad did not significantly attenuate internal carotid artery and the anterior cerebral artery vasospasm. In a rabbit model, tirilazad 1 mg kg^{-1}, given 12 h before the onset of experimental subarachnoid haemorrhage completely eliminated basilar artery vasospasm (seen in the placebo group), as assessed by morphometric analysis at 48 h post-injury.[79] In the same model, tirilazad administered 30 min after the onset of subarachnoid haemorrhage abolished basilar artery vasospasm as assessed by digital subtraction angiogram at 72 h.[88]

Vasospasm is the main treatable cause of death and disability following subarachnoid haemorrhage. Tirilazad is a potent scavenger of oxygen free radicals and an inhibitor of lipid peroxidation, which may play a central role in the development of vasospasm. However, more research is required before free radicals and reactions induced by them can be said to be the main cause of vasospasm.

Clinical data

Initial phase II trials with tirilazad in patients with subarachnoid haemorrhage were first carried out in 1995. Tirilazad was administered in doses of 0.6, 2 and 6 mg kg^{-1} day^{-1} i.v. for 10 days after SAH, in conjunction with nimodipine. No serious side effects were demonstrated at any of the three doses and there was a trend towards improvement in patient outcome in the 2 mg kg^{-1} day^{-1} group compared with the vehicle-controlled group at 3 months.[24]

More recently, there have been two large randomized, double-blind, controlled trials of tirilazad in patients with aneurysmal subarachnoid haemorrhage. The first involved neurosurgical centres in Europe, Australia and New Zealand, and enrolled 1023 patients. The patients were assigned randomly to receive either 0.6, 2 or 6 mg kg^{-1} day^{-1} of tirilazad or placebo. The patients also received nimodipine. Patients in the 6 mg kg^{-1} day^{-1} group had a greater frequency of good recovery on the Glasgow Coma Scale at 3 months (P=0.01) and a reduced mortality (P=0.01). There was also a reduction in symptomatic vasospasm in this group, but the difference was not statistically significant. The groups receiving 0.6 and 2 mg kg^{-1} day^{-1} showed no improvement. The benefits were predominantly in men.[46]

The second trial involved 902 patients enrolled from 54 North American neurosurgical centres. Patients were allocated randomly to three treatment groups, receiving either vehicle (control), 2 or 6 mg kg^{-1} day^{-1} tirilazad beginning within 48 h of a SAH and continued for 10 days. At 3 months, there was no significant difference in Glasgow Coma Score, mortality or employment status between the groups. There was also no significant difference in the incidence of vasospasm between the groups. When the mortality data were stratified according to gender and neurological grade on admission, men with grades IV and V in the 6 mg kg^{-1} day^{-1} group had a mortality of 5% compared with 33% in the control group, but this was not statistically significant (P=0.03).[25] The difference between the findings of the trials could be explained by differences in admission characteristics or management protocols, including the use of anticonvulsant medications.

A further study looked at 31 women with SAH allocated randomly to receive either vehicle or 15 mg kg^{-1} day^{-1} tirilazad for 10 days, and looked at more sensitive neuropsychological and psychosocial outcomes.[60] There was no difference in 3-month Glasgow Coma Scale or mortality in the two groups, although the tirilazad group showed less impairment of concentration, sustained attention and psychomotor speed ($P<0.02$), and debilitating fatigue ($P<0.01$). However, this study group is too small to make any conclusions and the results would have to be confirmed with larger patient groups.

A prospective double-blind, vehicle-controlled study[49] of high-dose tirilazad in 819 women with aneurysmal SAH randomized to receive 15 mg kg^{-1} tirilazad or placebo was conducted at 56 neurosurgical centres in Europe, Australia, New Zealand and South Africa, and concluded that high-dose tirilazad significantly reduced the incidence of symptomatic vasospasm from 33.3% in the placebo group to 24.8% in patients treated with tirilazad. However, there was no difference in the 3-month mortality rate. The more frequent use of other potentially effective rescue therapy (hypervolaemia, haemodilution and induced hypertension) in the placebo group (33.3%) compared with the tirilazad-treated patients (24.8%) may have been responsible for these contrasting observations between the two groups. In North America, a double-blind randomized study in women involving 832 patients[50] found that high-dose tirilazad 15 mg kg^{-1} day^{-1} significantly reduced the mortality from 43.4% to 24.6% among patients who were neurological grade IV or V on admission, confirming the beneficial effect observed in male patients in previous studies.[25 46] These latest findings may influence future management of high-grade cerebral aneurysms.

Discussion

It is well established that lipid peroxidation by free radicals is one of a number of biological mechanisms responsible for the secondary injury after traumatic or ischaemic injury to the CNS. The lazaroids are potent antioxidants, 100 times more potent than the corticosteroids, and therefore may be efficacious in the clinical management of acute CNS injury.

Experimental evidence in animal models of head injury, spinal cord injury, stroke and subarachnoid haemorrhage indicates that tirilazad obtunds secondary injury phenomena, promotes neurological recovery and improves outcome in these conditions. However, the evidence of the efficacy of tirilazad from phase III clinical trials is far from conclusive.

In the management of head trauma only one large clinical trial[54] has been carried out and showed no improvement in outcome. In spinal cord injury a 48-h infusion of tirilazad following an initial bolus of methylprednisolone was as effective as the established 24 h therapy with methylprednisolone.[11] However, tirilazad did not produce any additional benefit over standard steroid therapy either in terms of improved neurological outcome or in a lower rate of serious long-term complications. In addition, patients treated for 48 h with methylprednisolone or tirilazad commenced 3–8 h post-injury had a better outcome with methylprednisolone compared with tirilazad. The only large phase III trial in stroke patients showed no improvement in outcome with tirilazad.[65] In subarachnoid haemorrhage, a large phase III trial showed an improvement in outcome with 6 mg kg^{-1} day^{-1} tirilazad administered for 10 days.[46] The effect was most marked in men in whom mortality was reduced from 20 to 6%. However, a second American study[25] failed to show any significant benefit with tirilazad, although there was a trend towards a better outcome in men with grade IV–V subarachnoid haemorrhage. However, two recent studies utilizing a high-dose (15 mg kg^{-1} day^{-1}) regimen of tirilazad concluded that there was a significant reduction in both the incidence of vasospasm and the mortality rate among women with aneurysmal subarachnoid haemorrhage.

Two possible conclusions can be drawn from the disparity between the beneficial effects of tirilazad in pre-clinical animal studies compared with clinical trials. Firstly it may well be that tirilazad is ineffective as a cerebroprotectant after CNS injury in humans. It may be wrong to extrapolate the results of pre-clinical trials to humans because of controversy regarding the applicability of the animal model to human injury, the reproducibility of the model, and different responses of animals and humans to different drugs. The lazaroids do have limitations. Lipid peroxidation is only one of a number of biological mechanisms involved in the secondary injury, and other destructive secondary processes initiated by the primary insult such as the release of excitatory amino acid neurotransmitters and the loss of intracellular calcium homeostasis occur. The prevention of lipid peroxidation alone therefore may be ineffective in reducing the secondary injury. The poor penetration of the blood–brain barrier of the lazaroids and its localization in the vascular membrane may significantly limit their efficacy. Their ability to prevent lipid peroxidation may be dependent upon administration within minutes of the primary insult, something rarely possible in the clinical situation. It is notable that in the experimental studies the first dose of tirilazad was often administered within minutes of the primary insult, and in some studies the first dose was given pre-injury. However, in the clinical studies looking at spinal cord injury[11] and stroke,[65] approximately half the patients received their first dose of tirilazad more than 3 h post-injury, and this could contribute to the apparent lack of clinical efficacy.

However, the lack of efficacy of tirilazad in a number of clinical studies may have resulted from weaknesses within those studies. In the phase III study[54] looking at the effect of tirilazad compared with placebo in 1120 patients with head injuries, it was noted that there was a marked imbalance between the groups concerning the basic prognostic variables such as hypoxaemia and hypotension. It was also noted that there was a trend towards improved outcome in the small subgroup of patients with severe head injury associated with traumatic subarachnoid haemorrhage. It may be that a further study, using an alternate method of randomization and targeting populations with a higher risk of morbidity and mortality, would show an improved outcome with tirilazad.

It has also been suggested that the range of doses of tirilazad used in all these clinical studies (2–10 mg kg^{-1} day^{-1}) may be suboptimal, and the findings of the two important studies[49 50] of high-dose tirilazad in women with aneurysmal subarachnoid haemorrhage support this hypothesis. It may also explain the frequent finding that the beneficial effects of tirilazad are limited to men, in whom metabolism of the steroid moiety of tirilazad is less efficient compared with women. In the large phase III clinical study looking at tirilazad (6 mg kg^{-1} day^{-1} for 3 days) in stroke patients there was no improvement in outcome. However, a second smaller study looking at larger doses (10–15 mg kg^{-1} day^{-1} for 3 days) did show a reduction in mortality of 14%, although the study group was too small to make the difference significant. In the two large studies looking at the efficacy of tirilazad in the treatment of subarachnoid haemorrhage, one European, Australian and New Zealand study[46] has shown a marked improvement in outcome for men, whereas a second North American study[25] showed no difference in outcome. In the North American trial more than 80% of patients were on anticonvulsants, compared with 50% of patients in the first trial. The increased elimination of tirilazad caused by enzyme-inducing anticonvulsants could have resulted in lower blood concentrations of the study drug in North American patients. Higher doses of the drug might have obviated the gender difference in the European study and improved the results in the North American study. Recent multicentre studies of high-dose (15 mg kg^{-1} day^{-1}) tirilazad in women have indeed shown a significant reduction in the incidence of vasospasm associated with aneurysmal subarachnoid haemorrhage and the mortality in patients who were neurological grade IV or V on admission. These findings may well influence future treatment of high-grade cerebral aneurysms.

At the present time, the clinical evidence available is not strong enough to justify the routine use of tirilazad in the management of CNS trauma, ischaemia or subarachnoid haemorrhage. However, further studies using larger doses of tirilazad may show significant efficacy.[49 50] There is also increasing interest in using tirilazad in combination with thrombolytic agents in the management of ischaemic strokes.[74] Finally, there are now early animal studies investigating the pyrrolopyrimidines,[28] a group of antioxidants that have improved penetration of the blood–brain barrier and gain direct access to neural tissue.

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BJA

SHORT COMMUNICATIONS

Pharmacokinetic profile of epidurally administered methylnaltrexone, a novel peripheral opioid antagonist in a rabbit model

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Methylnaltrexone (MNTX) is the first peripheral opioid receptor antagonist used in man to treat acute and chronic opiate-mediated side-effects. We describe in a rabbit model the pharmacokinetics of epidurally administered MNTX 0.66 mg kg^{-1}, and we tested the hypothesis that epidurally administered MNTX does not penetrate the dura into the subarachnoid space. There were minimal concentrations of MNTX (40 ng ml^{-1}) detected in the CSF at 10 and 20 min and none thereafter in comparison with the high serum levels. The serum drug concentration–time profile fitted a two-compartment pharmacokinetic model. Further studies are warranted as epidurally administered MNTX may have the potential to reverse epidural opioid-mediated side-effects whilst preserving analgesia.

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Epidural opioid compounds are used for analgesia in clinical practice in patients suffering from acute and chronic pain. Common peripheral undesirable side-effects of epidural opioids include urinary retention, constipation and delayed gastric emptying, but the exact mechanisms remain unclear.[1] Epidural opioids may mediate these side-effects via a central, spinal and/or direct effect on local opioid receptors.[1] The relative contributions of each mechanism are unknown.

Methylnaltrexone (MNTX) is a quaternary opioid antagonist with limited ability to cross the blood–brain barrier. In man, intravenous MNTX has been shown to reverse morphine-induced delayed gastric emptying[2] and to reverse constipation due to chronic methadone use[3] without affecting centrally mediated analgesia. We postulated that if MNTX does not cross the dura it might have potential to reverse peripherally mediated side-effects of epidural opioids without affecting analgesia. Therefore, the purpose of this study was to describe the pharmacokinetics of epidurally administered MNTX and to test the hypothesis that epidurally administered MNTX does not penetrate the dura into the subarachnoid space (SAS).

Methods and results

With approval of the Animal Care and Research Committee of the University of Toronto, seven rabbits (3.3–3.5 kg) were anaesthetized with isoflurane in nitrous oxide and oxygen. A 22 g cannula was inserted in an ear vein and artery for blood sample collection and blood gas measurement. The trachea was intubated with a 4 mm (internal diameter) endotracheal tube and pancuronium 0.3 mg kg^{-1} was administered to produce muscle relaxation. The animals were placed prone on the operating table and the head was fixed in a modified stereotactic frame. The rabbits' lungs were ventilated (Harvard animal ventilator) to normocapnia and 10 ml kg^{-1} normal saline was administered every 30 min. The L_3 or L_4 vertebra was exposed via a midline lumbar incision by retracting the paraspinal muscles laterally. After laminectomy of one of the vertebra, a 22 g catheter was placed in the epidural space under direct vision. The cannula was inspected for the presence of CSF and aspirated. If CSF was detected the animal was discarded and replaced. After confirmation of placement in the epidural space the catheter was fixed in place with dental cement.

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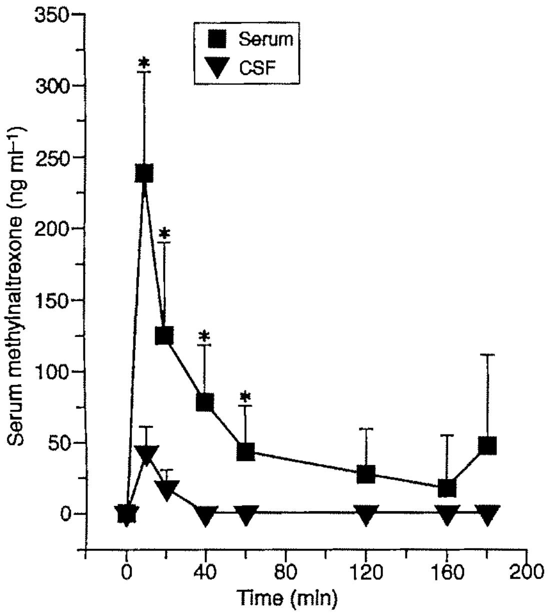

Fig 1 Plot of serum and CSF concentrations of methylnaltrexone (ng ml^{-1}) after epidural administration of methylnaltrexone 0.66 mg kg^{-1}. Data are mean (SD). *$P<0.05$, CSF *vs* serum (Mann–Whitney *U*-test).

A midline skin incision was made over the shaved back of the neck covering the occipital bone and cervical dorsum. The atlanto-occipital membrane was identified and a 22 g cannula was inserted in the base of the skull covering the cisterna magna, cephalad to the occipital–atlas junction. Spontaneous CSF flow was obtained and allowed to drain freely. The cannula was immobilized with dental cement. MNTX 0.66 mg kg^{-1} (Mallinckrodt Specialty Chemicals, St Louis, MO, USA) was administered in 1ml of normal saline via the epidural catheter and blood and CSF samples were taken 0, 3, 6, 10, 15, 20, 40, 60, 120 and 180 min after drug administration. The epidural dose of MNTX was chosen on the basis of previous results,[2 3] with the aim of administering a relatively high dose of MNTX. Animals were euthanized after 3 h by pentobarbital overdose. Blood samples were centrifuged, separated immediately and the serum and CSF sample was frozen at –80°C for later analysis by high-performance liquid chromatography. Using the modified procedure from the method of Kim *et al.*,[4] standard curves of MNTX were run for each set of samples. The lower limit of detection was 2 ng ml^{-1}. Pharmacokinetic parameters for MNTX were calculated using WinNonlin™ (2.1 Scientific Consulting, Mountain View, CA, USA).

Seven rabbits were enrolled in the study, but data from two were excluded due to difficulty in CSF or blood sampling techniques. Results are expressed as mean (SD) unless stated otherwise. The mean weight of the animals was 3.5 (0.3) kg. The serum drug concentration –time profile for each animal fitted a biexpontential function. Therefore, the disposition of epidural MNTX could be described by a two-compartment model in which the drug is eliminated from the central compartment. The mean serum and CSF MNTX concentrations determined during the duration of the study are shown in Fig. 1. There were minimal amounts of MNTX detected in the CSF at up to 20 min and none thereafter. The following pharmacokinetic data were calculated: area under the curve [AUC$_{0-240}$ 11920 (3892) ng min^{-1} ml^{-1}], peak concentration [C$_{max}$ 215 (35) ng^{-1} ml^{-1}], time to maximum concentration (T$_{max}$ 10 min), total volume of distribution [Vz 5199 (1199) ml kg^{-1}], total body clearance [CL 86 (26) ml min^{-1} kg^{-1}] and β half-life [T$_{\frac{1}{2}}$ β 74.96 (35) min^{-1}]

Comment

This is the first study to describe the pharmacokinetics of epidurally administered MNTX. After epidural administration, minimal concentrations of the drug were detected in the CSF compared with plasma. Previous studies in animals and man showed the ratio of peak CSF:serum morphine levels are of the order of 35:1 after epidural morphine administration.[5] However, in this study the CSF:serum ratio was reversed to 1:5 after high-dose epidural MNTX, suggesting that high doses of epidural MNTX do not appear to cross the dural membrane significantly and would not have clinical implications. Its relative lack of dural penetration may be due to the presence of a bulky quaternary charged N_2 atom in the drug molecule. The low concentration of MNTX seen in the CNS was produced by the administration of doses very much larger than those expected to be used clinically. MNTX has significantly lower affinity for the opioid receptor than naltrexone[6] and the maximum concentration detected in the CSF is unlikely to have clinical implications. However, evaluation of this low CNS penetration would need to be studied in the clinical setting. Therefore, we postulate that, during coadministration of centrally acting opioids and MNTX in the epidural space, MNTX absorbed into the vascular compartment will act only on peripheral opioid receptor while maintaining centrally mediated analgesia.

After epidural administration of MNTX 0.66 mg kg^{-1}, peak serum values were greater than 200 ng ml^{-1}. These systemic drug levels may possibly be of therapeutic significance. In patients on chronic opioid therapy who received i.v. MNTX in doses up to 0.35 mg kg^{-1} over 1 min, rapid laxation was induced without evidence of withdrawal or diminished analgesia. Peak plasma levels of 162 (237) ng ml^{-1} were observed without side-effects in that group.[3]

In conclusion, epidurally administered MNTX does not appear to gain significant access to the CSF. Further studies are warranted as epidurally administered MNTX may have potential to reverse epidural opioid-mediated side-effects whilst preserving analgesia.

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Influence of head and neck position on cuff position and oropharyngeal sealing pressure with the laryngeal mask airway in children

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We studied how head and neck position affect the cuff position and oropharyngeal sealing pressures of the laryngeal mask airways (LMAs) in children. We studied 39 non-paralyzed healthy children aged 1.5–8.0 yr, weighing 10.3–27.0 kg, managed with size 2 or 2.5 LMAs during elective surgery. Head and neck movements did not adversely affect airway patency in 97% of patients. One child developed apparent airway obstruction with head and neck flexion, which was relieved in the neutral position. Oropharyngeal sealing pressure was significantly greater during neck flexion compared with the neutral position ($P<0.02$). Fibreoptic examination revealed that the epiglottis covered a larger area of the LMA aperture during neck flexion, compared with the neutral position ($P<0.02$).

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Keywords: intubation tracheal; equipment, mask anaesthesia

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The laryngeal mask airway (LMA[†]) is used for paediatric surgery with different head and neck positions, such as extension of the neck for adenotonsillectomy,[1] and rotation of the head for myryngotomy.[2] Studies of children with their head and neck in neutral position, assessing the position of the LMA fibreoptic[3–5] or radiological[6] examination, found that well functioning LMAs were not necessarily ideally anatomically, placed. Fibreoptic examination of the LMA position showed that the epiglottis occupied a larger area within the LMA aperture in children than in adults.[4 5] These observations suggest that head and neck movement could distort the oropharyngeal space, and affect anatomical position and function of the LMA more in children than in adults.

A study of adult patients[7] showed little influence of head and neck position on cuff position and oropharyngeal leak pressure of the LMA, but no studies have been done in children.

We measured how head and neck movement changed the cuff position and oropharyngeal sealing pressure of the LMA in children patients.

Methods and results

After obtaining Ethics Committee approval and informed consent from the parents, we studied ASA physical status I paediatric patients who were managed with size 2 or 2.5 LMAs during elective urological surgery.

Anaesthesia was induced via a facemask with 5% sevoflurane and nitrous oxide in 65% oxygen. After obtaining sufficient depth of anaesthesia, LMAs were inserted by well-trained anaesthesiologists using the technique recommended by the manufacturer without the use of neuromuscular blocking agents. The size of LMA was chosen according to the manufacturer's guideline (size 2 for 10–20 kg, and size 2.5 for 20–30 kg). The intra-cuff pressure was adjusted to 60 cmH_2O using an ergonomic pressure gauge (Hi-Lo™ Hand Pressure Gauge, Mallinckrodt Medical, Germany). General anaesthesia was maintained with oxygen, 65% nitrous oxide, and sevoflurane. Patients breathed spontaneously through the LMA for the duration of surgery. In all patients regional anaesthesia (caudal block or epidural block) was performed.

[†] LMA is the property of Intavent Limited.

At the end of surgery, the intra-cuff pressure of the LMA was adjusted to 60 cmH_2O again with the head and neck in the neutral position. Anaesthesia was maintained with sevoflurane 2%, nitrous oxide 65%, and oxygen. The head and neck position was then changed successively to the following positions; neutral, maximal flexion, maximal extension (about 45°, each) and about 90° rotation to the left and right. In each position, after 30–60 s of a stable period, oropharyngeal sealing pressures and fibreoptic images were recorded. To assess sealing pressure, the expiratory valve of the circle breathing system was closed and fresh gas flow adjusted to 3 litre min^{-1}. Pressure in the breathing circuit increased until airway pressure reached equilibrium. The airway pressure was measured with an aneroid manometer attached to the breathing circuit and recorded as oropharyngeal sealing pressure.[8] During these measurements the position of the head and neck was hidden from the observer. After this the expiratory valve was re-opened and a fibreoptic scope was passed to a position just proximal to the mask aperture bars and the view was recorded on videotape. A second anaesthetist, not aware of the position of the head and neck, scored the views on videotape as follows; 1: the view through aperture bars completely covered with anterior epiglottis, but LMA function adequate; 2: anterior epiglottis covering more than 2/3 of the view in diameter; 3: anterior epiglottis covering more than 1/3, but less than 2/3 of the view in diameter; and 4: anterior epiglottis covering less than 1/3 of the view in diameter.

A factorial analysis of variance was used to assess the differences in the oropharyngeal leak pressure among groups. Post-hoc testing of multiple comparisons was performed with Scheffé's procedure. The fibreoptic scores were analysed using the Kruskal–Wallis rank test for comparison among groups and the Mann–Whitney *U* test for the comparison between neutral position and other groups. $P<0.05$ was accepted as statistically significant.

Thirty-nine patients, ages from 1.5 to 8.0 yr (mean 4.0 yr) and weighing between 10.3 and 27.0 kg (mean 15.7 kg) were enrolled in this study. Thirty-one size 2 LMAs, and eight size 2.5 LMAs were used.

The movement of the head and neck did not adversely affect the airway patency in 38 of the 39 patients and these patients could breathe spontaneously in all head and neck positions. One 3-yr-old child weighing 14 kg, managed with a size 2 LMA developed airway obstruction during neck flexion, which was relieved in the neutral position. The results are summarized in Table 1.

Table 1 Oropharyngeal sealing pressure and fibreoptic score in the five head and neck positions. $^*P<0.05$ *vs* neutral position

Head and neck positions	**Sealing pressure (cm H_2O) (mean (SD))**	**Fibreoptic score (4/3/2/1)**
Neutral	20.3 (7.4)	10/20/7/2
Flexion	26.8 (10.3)*	4/17/11/6*
Extension	19.1 (7.2)	12/20/5/2
Ation (right)	22.7 (7.0)	21/11/5/2
Rotation (left)	22.6 (7.5)	20/14/4/1

Comment

In agreement with previous reports,[3–6] we also found that the epiglottis occupied a considerable area of the aperture of the LMA, and that airway patency was well maintained in most patients with any head and neck position, during breathing.

The fibreoptic score proposed by Brimacombe[9] has been used for the assessment of LMA positioning in many studies, mainly with adult patients. However, this score did not seem suitable for the assessment of LMA positioning in paediatric patients. As the epiglottis occupied a considerable area in the LMA aperture in the majority of children, such fibreoptic findings would be classified into the same score if this method were used. We used an alternative scoring system to express the extent that the epiglottis occupied the LMA aperture.

In the current study, the fibreoptic score was less during neck flexion than in the neutral position, with the epiglottis filling more of the aperture view. Neck flexion could increase the posterior deflection of the epiglottis. Sealing pressure with neck flexion was greater than in the neutral position in agreement with previous studies of adults.[7] Neck flexion could reduce the longitudinal tension in the anterior pharyngeal muscles, allowing them to settle down onto the mask to form a better seal.

One child developed an apparent airway obstruction with neck flexion, which could be relieved in the neutral position. Together with the fact that the epiglottis fills the aperture of the LMA more in this position, head flexion may possibly jeopardize LMA function, but further study of this is needed.

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Waste gas exposure to sevoflurane and nitrous oxide during anaesthesia using the oesophageal–tracheal Combitube small adult™

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Exposure to sevoflurane (SEV) and nitrous oxide during ventilation using a Combitube (37Fr) small adult (SA) was compared with waste gas exposure using conventional endotracheal tubes. Trace concentrations of SEV and nitrous oxide were assessed using a direct reading spectrometer during 40 gynaecological laparoscopic procedures under general anaesthesia. Measurements were made at the patients' mouth and in the anaesthetists' breathing zone. Mean (SD) concentrations of SEV and nitrous oxide measured at the patients' mouth were comparable in the Combitube SA (SEV 0.6 (0.2) p.p.m.; nitrous oxide 9.7 (8.5) p.p.m.) and endotracheal tube group (SEV 1.2 (0.8) p.p.m.; nitrous oxide 17.2 (10.6) p.p.m.). These values caused comparable contamination of the anaesthetists' breathing zone (SEV 0.6 (0.2) p.p.m. and nitrous oxide 4.3 (3.7) p.p.m. for the Combitube SA group, compared with SEV 0.5 (0.2) p.p.m. and nitrous oxide 4.1 (1.8) p.p.m. for the endotracheal tube group). We conclude that the use of the Combitube SA during positive pressure ventilation is not necessarily associated with increased waste gas exposure, especially when air conditioning and scavenging devices are available.

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Because the health consequences of environmental exposure to anaesthetic vapour[1] are controversial, US and European health authorities recommend limits ranging between 2 and 75 p.p.m. for volatile anaesthetic exposure and between 25 and 100 p.p.m. for nitrous oxide to minimize health hazards.[2] The European community has yet to establish exposure limits for sevoflurane (SEV), but the likely level is expected to be similar to that of isoflurane or enflurane ranging between 10 and 20 p.p.m.

During general anaesthesia, more contamination occurs when unsealed airway devices and/or high concentrations of inhalational anaesthetics are used.[2–5] In particular the laryngeal mask airway (LMA) or the oesophageal–tracheal Combitube™ (ETC) could increase contamination when used for ventilatory support during surgical procedures commonly associated with elevated airway pressures being increased (e.g. laparoscopic surgery with peritoneal carbon dioxide inflation and steep Trendelenburg position). The ETC has only been used infrequently during elective surgery,[6] because the standard ETC model (41Fr) is a rather large and potentially traumatic device. Therefore, the small adult (SA) model (Combitube (37Fr) SA™; Kendall; Gosport, Hampshire, UK) has been introduced in clinical practice[7] and is a valuable alternative airway for mechanical ventilation during routine surgery in our hospital.

Because there is a lack of data about the environmental safety of the new airway device, we planned a randomized controlled study to measure operating room air contamination by waste anaesthetic gases during Combitube SA™ ventilation for gynaecological laparoscopy, compared with a second group of patients managed by conventional tracheal intubation.

Methods and results

After approval by the Institutional Ethics Committee and obtaining patients written informed consent, 40 otherwise healthy patients (ASA physical status I–II) scheduled for elective laparoscopic gynaecological procedures were recruited.

Using a computer generated random list, treatment assignments (ETC, n=20 or endotracheal tube (ETT), n=20) were contained in sequentially ordered sealed envelopes, which were opened just before anaesthesia induction. Induction, maintenance, and emergence from anaesthesia were performed in the operating room. Anaesthesia was induced with propofol 1.5–3.0 mg kg^{-1}, neuromuscular block obtained with vecuronium 0.1 mg kg^{-1}, and anaesthesia was maintained with i.v. fentanyl, SEV, and 65% nitrous oxide in oxygen with a fresh gas flow of 3 litre min^{-1}. All tubes were connected without using swivels to the anaesthesia machine (Cicero, Draeger AG, Germany). The waste gas outlet of this machine was connected to a scavenging system which in turn was connected to the hospital vacuum system at aspiration rates of 45 litre min^{-1}. Inspiratory and end-expiratory SEV and nitrous oxide concentrations and ventilatory variables were recorded using the anaesthesia machine's build-in monitoring system.

Intermittent positive pressure ventilation (IPPV) with the administration of SEV and nitrous oxide was started after insertion of either the Combitube SA™ or tracheal tube. Using direct laryngoscopy, a Combitube SA™ (37Fr) was oesophageally inserted by the same anaesthetist in all group ETC patients. After oesophageal placement of the ETC, the oropharyngeal balloon was inflated with air volumes according to the formula: balloon volume (ml)=height (cm)–100.[6] Thereafter, the distal oesophageal cuff was inflated with 8 ml of air and supraglottic ventilation was started via the longer blue lumen of the ETC. In group ETT, conventional endotracheal tubes (Portex, Vienna, Austria) with an internal diameter of 7.0 mm were used. Cuff pressure was kept within the range of 20–30 cm H_2O using an Endotest (Ruesch, Germany) manometer.

The study was conducted in a room that had 20-air exchanges h^{-1}, with all ventilation being fresh air. Ambient gas was continuously sampled from two different locations using a Teflon® tube (Merck, Vienna, Austria). One sampling probe was fixed 2–3 cm above the patient's mouth and a second one fixed at the shoulder of the anaesthetist (breathing zone). Operating room anaesthetic vapour concentrations of SEV, and nitrous oxide samples were assessed at 1 min intervals using a Brüel and Kjaer (Naerum, Denmark) spectrometer connected to a multipoint sampler. Before starting the study, the system was calibrated for each gas, for example with 20.8 p.p.m. SEV in pure nitrogen (Kaiser, Vienna, Austria) to provide an accuracy of ±2% over the entire relevant range. During the calibration process, the system software compensated for potential confounding effects of humidity, air pressure and temperature, SEV, nitrous oxide, isopropanol, water and carbon dioxide.

The occupational exposure standards were calculated according to the UK Occupational Exposure Limits 1999.[8] Data are separately presented for each measurement point as average exposure of each anaesthesia as medians with 10th, 25th, 75th, and 90th percentiles. Values were compared using non-parametric tests (Mann–Whitney U test) using SPSS 6.1 (Macintosh OS 8.5) and a P<0.05 was considered statistically significant.

Patients' characteristics were comparable between the groups. All patients in both groups were either oesophageally or tracheally intubated at the first attempt, ventilatory support was sufficient and no differences in ventilatory and respiratory variables were observed between the groups. No respiratory or cardiopulmonary complications occurred in either group.

Average (mean (SD)) vaporizer settings of the anaesthesia machine were 1.1 (0.3) vol% in group ETC and 1.2 (0.2) vol% in group ETT. The resulting mean end-tidal SEV concentrations were 1.0 (0.2) vol% or 0.6 (0.3) MAC h^{-1} in group ETC vs. 1.0 (0.2) vol% or 0.5 (0.2) MAC h^{-1} in group ETT (P=n.s. between the groups).

The distributions of the average waste anaesthetic gas concentrations observed during each procedure are presented as box-plots (median 10th, 25th, 75th and 90th percentile) in Fig. 1. The mean (SD) trace gas concentrations at the patients' mouth observed during anaesthesia were 0.6 (0.2) p.p.m. SEV and 9.7 (8.5) p.p.m. nitrous oxide using a ETC. This gave an exposure of the anaesthetist to 0.6 (0.2) p.p.m. SEV and 4.3 (3.7) p.p.m. nitrous oxide over a period of about 60 min lasting each anaesthesia.

During anaesthesia and ventilatory support using tracheal intubation, 1.2 (0.8) p.p.m. SEV and 17.2 (10.6) p.p.m. nitrous oxide were found at the patients' mouth giving an exposure of the anaesthetist of 0.5 (0.2) p.p.m. SEV and 4.1 (1.8) p.p.m. nitrous oxide over the time of anaesthesia.

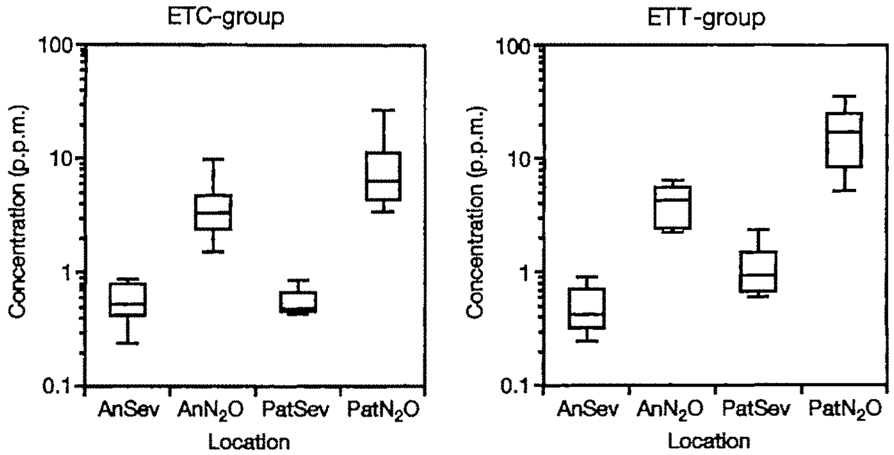

Fig 1 Distribution of average SEV and nitrous oxide concentrations for each group and patient at each measurement point (median —, 10th, 25th, 75th and 90th percentile). AnSev represents the location anaesthesist's breathing zone and measured substance SEV, AnN_2O nitrous oxide at the location anaesthesist's breathing zone, PatSev and $PatN_2O$ SEV and nitrous oxide, respectively, at the location patient's mouth.

No significant differences between ETC and ETT were recorded for both substances measured at the patient's mouth, and at the breathing zone of the anaesthetist.

Comment

We found that the Combitube SA™ gave a patent airway with an adequate seal during controlled mechanical ventilation for gynaecological laparoscopy. Although the ETC provides only supraglottic ventilation and does not seal the trachea directly, the waste gas exposure was comparable with tracheal intubation. Gynaecological laparoscopic procedures were chosen for the environmental measurements, because these procedures represent a special challenge for airway management and ventilatory support[6] with an increased risk of gas leakage because of the elevated intra-abdominal and airway pressures. Because the ETC does not seal the trachea directly, we expected leakage and significant environmental waste anaesthetic gas contamination, especially at the patients' mouth.

Most international health authorities set occupational standards ranging from low to relatively high levels, demonstrating their uncertainty about the risks of chronic exposure. Chromosomal damage can be detected even when exposure was well within the recommended standards, but no long-term outcome of these changes could be established. Although these studies investigated the effects of a combined exposure to isoflurane and nitrous oxide, the amount of waste anaesthetic gases during different operating room settings and anaesthetic procedures should be assessed.

We conclude that using the Combitube SA™ in patients undergoing positive pressure ventilation is not necessarily associated with greater waste gas exposure, especially when air conditioning and scavenging devices are available.

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Effect of two anaesthetic regimens on airway nitric oxide production in horses

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There is evidence that halothane inhibits nitric oxide synthase *in vitro*, but the effect of intravenous anaesthetic agents is less clear. This study was undertaken to compare the rate of exhaled nitric oxide production ($\dot{V}_{NO}$) in spontaneously breathing horses anaesthetized with halothane or an intravenous regimen. Seven adult horses were studied twice in random order. After premedication with romifidine 100 µg kg^{-1}, anaesthesia was induced with ketamine 2.2 mg kg^{-1} and maintained with halothane in oxygen (HA) or by an intravenous infusion of ketamine, guaiphenesin and romifidine (IV). Inhaled and exhaled nitric oxide (NO) concentrations, respiratory minute ventilation ($\dot{V}_E$), pulmonary artery pressure (P_{PA}), fractional inspired oxygen concentration ($F_{I_{O_2}}$), end-tidal carbon dioxide concentration (E'_{CO_2}), cardiac output ($\dot{Q}$) and partial pressures of oxygen and carbon dioxide in arterial blood (Pa_{O_2}, Pa_{CO_2}) were measured. Exhaled nitric oxide production rate was significantly lower (40 min, $P<0.01$; 60 min, $P<0.02$) during HA [40 min, 1.4 (SD 1.4) pmol l^{-1} kg^{-1} min^{-1}; 60 min, 0.7 (0.7) pmol l^{-1} kg^{-1} min^{-1}] than during IV [40 min, 9.3 (9.9) pmol l^{-1} kg^{-1} min^{-1}; 60 min, 12.5 (13.3) pmol l^{-1} kg^{-1} min^{-1}). Mean pulmonary artery pressure was significantly higher (40 min, $P<0.01$; 60 min, $P<0.001$) during HA [40 min, 5.9 (1.1) kPa; 60 min, 5.9 (0.9) kPa] compared with IV (40 min, 4.4 (0.4) kPa; 60 min, 4.4 (0.5) kPa]. NO is reduced in the exhalate of horses anaesthetized with halothane compared with an intravenous regimen. It is suggested that increased mean pulmonary artery pressure during halothane anaesthesia may be linked to the differences in NO production.

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Keywords: horse; anaesthesia; pharmacology, nitric oxide; anaesthetics volatile, halothane

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Nitric oxide (NO) has been shown to regulate vascular tone in both the systemic and the pulmonary circulation and has been detected in the exhalate of a number of species, including the horse.[1] In the standing conscious horse, infusion of the NO donor nitroglycerine has been shown to reduce pulmonary vascular pressures.[2] Similarly, infusion of the nitric oxide synthase (NOS) inhibitor L-NAME has been shown to increase resting pulmonary arterial pressures.[3] A number of studies in other species have shown that halothane attenuates endothelium-dependent pulmonary vasodilatation, which may or may not involve NO, both *in vitro*[4] and *in vivo*.[5] The interaction of NOS with intravenous anaesthetics is less clear. For example, propofol has been shown to increase NO release from cultured porcine endothelial cells[6] whilst a number of other intravenous anaesthetic agents have been reported to decrease brain NOS activity *in vitro*.[7] The hypothesis was that horses anaesthetized with halothane would exhibit lower exhaled NO concentrations than horses anaesthetized with a total intravenous regimen.

Methods and results

The study was carried out under Home Office licence PPL 80/1017 and was approved by the Ethics Committee of the Animal Health Trust. Seven healthy adult horses [one female, six castrated males; weight 508 (SD 33) kg; median age 4 yr, range 3–18 yr] were studied on two occasions. Four horses underwent procedure HA first and three underwent procedure IV (see below). Food, but not water, was withheld from 20.00 h on the day preceding each study. In both procedures, the horses were premedicated with romifidine 100 µg kg^{-1} and anaesthesia was induced with ketamine 2.2 mg kg^{-1}. During procedure HA, anaesthesia was maintained by halothane at an end-tidal concentration of 0.9%. In procedure IV, guaiphenesin 50 mg kg^{-1} was administered as a bolus immediately after induction and anaesthesia was maintained by an infusion of romifidine 82 μg kg^{-1} h^{-1} and ketamine 6.6 mg kg^{-1} h^{-1}. Guaiphenesin was also infused at the rate of 100 mg kg^{-1} h^{-1} for the first 30 min of anaesthesia and the rate was then reduced to 60 mg kg^{-1} h^{-1}. The trachea was intubated with a 30 mm cuffed tracheal tube and the animals breathed spontaneously from a large-animal circle absorber with a leak (a partial rebreathing circuit) supplied with oxygen at a fresh gas flow rate of 10 litre min^{-1}. Carbon dioxide was absorbed from the expired gas using soda lime. The distal end of the tracheal tube and the circle Y-piece were fitted with adaptors to allow insertion of a pneumotachometer and the collection of expired gases.

Measurements of pulmonary artery pressure (P_{PA}) were made using a strain-gauge transducer mounted on the tip of a 150 cm, 8F, woven Dacron catheter (Gaeltec, Dunvegan, Isle of Skye, UK) interfaced to a pressure amplifier (Model 13–4615–52; Gould, Essex, UK). The catheter was introduced via an 8F arterial sheath introducer (Haemaquet-Steri Lock; Bard, Crawley, UK) into the right jugular vein. Cardiac output ($\dot{Q}$) was measured using transoesophageal Doppler echocardiography. Arterial blood oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions were measured at 37°C with a blood gas analyser (model 248; Chiron Diagnostics, Essex, UK).

Respiratory airflow was measured with a Fleisch No. 3 heated pneumotachometer connected to a differential pressure transducer (DP41–14; Validyne, Northridge, CA, USA). The pneumotachometer was calibrated with a known volume (7 litres) from a calibrated volume syringe (Series 4900; Hans Rudolph, Kansas City, KA, USA). Respired gases (oxygen, nitrogen, carbon dioxide and halothane) were measured continuously with a respiratory mass spectrometer (MGA200; Morgan Medical Ltd, Rainham, UK). The mass spectrometer was calibrated with two certified gas mixtures representing the range to be encountered during the studies (BOC Speciality Gases, Guildford, UK). The sampling capillary was inserted into the circuit distal to the pneumotachometer to sample both inspired and expired gases.

Concentrations of NO (p.p.b.) in the inspired and expired limbs of the circuit approximately 15 cm on each side of the Y-piece were measured with a dedicated chemiluminescence analyser (270B; Sievers Instruments, Boulder, CO, USA). Measurements of both inhaled and exhaled NO were made over 30 s during periods of regular breathing to reduce the effect of variations throughout each breath in NO concentration and the inherent variation of the analyser, which in the HA procedure was operating near the manufacturer's reported lower limit of sensitivity (5 p.p.b.). This approach was considered preferable to making single point measurements of NO concentration. As the gas in the expired limb continues to be sampled by the NO analyser during the subsequent period of inspiration, this approach could potentially bias the average exhaled NO concentration according to the NO concentration in the last portion of gas exhaled. In order to reduce this error, measurements were made only during periods of regular breathing, without periods of apnoea between breaths, which would have prolonged the period in which the end-tidal NO continued to be sampled. In addition, the exhaled NO concentration varied minimally throughout exhalation. Net NO production was estimated by subtracting inspired NO concentration from expired NO concentration. Before each measurement of inspired and expired NO, a two-point calibration was performed with zero (100% nitrogen) and mixtures made by volume dilution of a certified NO standard mixture (400 p.p.b.; BOC Speciality Gases).

To determine that halothane did not affect the NO analyser, the anaesthetic system was set up without being connected to a horse and the connection to the tracheal tube was capped. The system was filled and flushed with oxygen and, once the oxygen concentration was above 98%, the flow rate was adjusted to 10 litre min^{-1}. Nitric oxide from a cylinder at 1000 p.p.m. (BOC Speciality Gases) was metered into the circuit to achieve a concentration at the Y-piece of ~5 p.p.m., as determined by the NO analyser. Halothane was then added to the circuit to a maximum concentration of 3%, as determined by a calibrated piezoelectric agent monitor (Lamtec 605; Pneupac, Luton, UK), with the sample line positioned at the Y-piece of the breathing circuit.

In order to express respired gas volumes according to BTPS (body temperature and pressure, saturated) convention, gas was drawn continuously from the inspiratory limb of the circuit by a vacuum pump (flow rate <3 litre min^{-1}) across a combined temperature and humidity sensor (HMP35B; Vaisala, Cambridge, UK). A second probe in the operating theatre recorded ambient temperature and humidity.

The voltage signals from the pressure amplifier, pneumotachometer and NO analyser were digitized at 500 Hz and analysed with a commercial data acquisition and analysis system (Po-Ne-Mah; Linton Instrumentation, Diss, UK). Measurements of diastolic ($P_{PA\ DIA}$), systolic ($P_{PA\ SYS}$) and mean pulmonary artery pressure ($P_{PA\ MEAN}$), respiratory minute ventilation ($\dot{V}_E$) and net NO production were made at 40 and 60 min of anaesthesia in both groups. Effects of time and treatment were investigated using analysis of variance and Tukey's test. Where data were not normally distributed (net exhaled NO concentration, $\dot{V}_{NO}$, Pa_{O_2} and $\dot{Q}$), they were transformed by conversion to the natural logarithm before statistical analysis.

Net exhaled NO concentration, tidal volume, respiratory minute ventilation, NO production rate, fractional inspired oxygen, end-tidal carbon dioxide, partial pressures of oxygen and carbon dioxide in arterial blood, cardiac output and pulmonary artery pressures after 40 and 60 min of HA and IV anaesthesia are shown in Table 1. There was no significant within-group difference between the 40 and

Table 1 Net exhaled (exhaled–inhaled) nitric oxide concentration (NO), tidal volume (V_T), mass specific respiratory minute ventilation ($\dot{V}_E$), NO production rate ($\dot{V}_{NO}$), fractional inspired oxygen (FI_{O_2}), end-tidal carbon dioxide (E'_{CO_2}), arterial oxygen and carbon dioxide tensions (Pa_{O_2}, Pa_{CO_2}), cardiac output ($\dot{Q}$) and systolic ($P_{PA\ SYS}$), diastolic ($P_{PA\ DIA}$) and mean ($P_{PA\ MEAN}$) pulmonary artery pressures at 40 and 60 min of anaesthesia with halothane (HA) or an intravenous regimen (IV). Data are mean (SD), $n=7$. IV was significantly different from HA at the corresponding time: $^*P<0.05$; $^\dagger P<0.02$; $^\ddagger P<0.01$; $^\S P<0.001$

	Duration of anaesthesia			
	40 min		**60 min**	
	HA	**IV**	**HA**	**IV**
Net exhaled NO (p.p.b.)	0.4 (1.0)	2.9 (2.3)†	0.4 (0.4	3.9 (2.9)†
V_T (litres), BTPS	5.0 (1.5)	4.7 (0.8)	5.1 (1.7)	4.9 (0.7)
$\dot{V}_E$ (ml kg^{-1} min^{-1}), BTPS	86 (35)	108 (45)*	82 (26)	109 (51)*
$\dot{V}_{NO}$ (pmol l^{-1} kg^{-1} min^{-1}), BTPS	1.4 (1.4)	9.3 (9.9)‡	0.7 (0.7)	12.5 (13.3)†
FI_{O_2} (%)	94.4 (2.5)	96.6 (3.3)	96.7 (1.4)	97.6 (2.9)
E'_{CO_2} (%)	6.4 (1.1)	6.2 (0.9)	6.2 (0.6)	6.2 (0.6)
Pa_{O_2} (kPa)	46.7 (10.8)	48.9 (8.4)	47.9 (11.2)	50.1 (8.5)
Pa_{CO_2} (kPa)	8.1 (0.9)	7.7 (0.7)	8.8 (1.3)	7.7 (0.5)
$\dot{Q}$ (litre min^{-1})	30 (10)	32 (6)	35 (13)	33 (7)
$P_{PA\ SYS}$ (kPa)	7.0 (1.1)	5.7 (0.6)‡	7.0 (1.0)	5.6 (0.6)‡
$P_{PA\ DIA}$ (kPa)	5.0 (1.1)	3.6 (0.4)‡	5.0 (0.9)	3.5 (0.3)§
$P_{PA\ MEAN}$ (kPa)	5.9 (1.1)	4.4 (0.4)‡	5.9 (0.9)	4.4 (0.5)§

60 min time points for any of the measurements with either technique.

Net exhaled NO, $\dot{V}_E$ and $\dot{V}_{NO}$ were significantly higher and systolic, diastolic and mean pulmonary artery pressures were significantly lower in the IV than in the HA group. During *in vitro* testing, the NO concentration in the circle, when not connected to a horse, showed no change during or after addition of halothane. Thus, it was concluded that the reduced exhaled NO is unlikely to be an artefact due to an effect of halothane on the NO analyser.

Comment

Previously we have reported mean exhaled NO concentrations of 1–3 p.p.b. in conscious, unsedated, nasal-breathing healthy adult horses at rest.[1] In the present study, net exhaled NO concentrations in the IV procedure were similar to those in resting horses, although the rate of NO production was reduced because of lower minute ventilation. Net exhaled NO concentration and the rate of NO production during halothane anaesthesia were lower than when the same horses where anaesthetized with an intravenous regimen. The most simple explanation for a reduction in exhaled NO concentration would be an inhibition of NOS. However, there is currently little evidence to support the contention that halothane inhibits NOS directly.

Reduced airway NO production has also been reported in association with increased inspired carbon dioxide, but in the present study there was no significant difference in arterial carbon dioxide between procedures. It has also been suggested that the degree of lung distension may effect NO production in anaesthetized rabbits[8] and exercising horses.[1] Tidal volume was not different between anaesthetic regimens, although minute ventilation was significantly higher with the IV procedure. A change in functional residual capacity could have occurred, but there is no reason to expect that this would have been different between procedures. Measured exhaled NO could have been reduced if removal of NO by the lower airways was enhanced, although how this might be mediated is unclear.

NO has been shown to be involved in the regulation of pulmonary vascular tone in both systemic and pulmonary circulations in many species, including the horse.[2 3] A consequence of reduced NO production or increased removal during anaesthesia might therefore be expected to be manifested as an increase in pulmonary arterial pressure. In the present study, mean pulmonary artery pressure was greater in the HA group than in the IV group. Other mechanisms that could have resulted in a higher mean pulmonary artery pressure include increased cardiac output and arterial carbon dioxide tension, although in the present study these were not different between procedures. Alternatively, the lower pulmonary pressures in the IV procedure could have been due to the intravenous drug mixture *per se*, but romifidine, an α_2-adrenoreceptor agonist, usually increases systemic vascular resistance and pulmonary artery pressures in conscious horses. In addition, with the IV procedure mean pulmonary artery pressures were similar to those in conscious, unsedated horses at rest.

In the present study we have shown that NO production is reduced in horses anaesthetized with halothane compared with an intravenous regimen, and that this is associated with an increase in mean pulmonary artery pressure. We have also shown in a separate study that administration of exogenous inhaled NO (10 p.p.m.) did not reduce pulmonary artery pressure during halothane anaesthesia.[9] Therefore, the present study supports the hypothesis that halothane causes *in vivo* suppression of NOS. However, failure of exogenous inhaled NO to reduce pulmonary artery pressure during halothane anaesthesia implies either that NO is not important for the regulation of pulmonary vascular tone under these conditions or that there is inhibition of the action of NO, possibly through interference with cGMP-mediated relaxation.[10] In conclusion, it is possible that the increased mean pulmonary artery pressure in these horses during halothane anaesthesia may be linked to the observed differences in NO production.

Acknowledgements

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Use of cisatracurium during fast-track cardiac surgery

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We prospectively studied spontaneous recovery from cisatracurium-induced neuromuscular block in 18 patients scheduled for cardiac surgery, and its suitability for fast-track cardiac surgery. Neuromuscular block was induced by an i.v. bolus (range 0.15–0.3 mg kg^{-1}) and maintained by a continuous infusion (range 1.1–3.2 µg kg^{-1} min^{-1}) of cisatracurium until sternal closure. In the intensive care unit (ICU), spontaneous recovery was evaluated by the train-of-four (TOF) ratio measured at the adductor pollicis muscle. The ICU medical staff were unaware of the TOF ratios until sedation was stopped. At that time, if the TOF ratio was less than 0.9, sedation was recommenced. On arrival in ICU, all patients had residual paralysis. The mean time to reaching a TOF ratio of at least 0.9 was 102 min (range 74–144 min) after discontinuation of the cisatracurium infusion. Fifteen patients (83%) were successfully extubated during the first 8 h after stopping the cisatracurium infusion. Only one patient showed residual paralysis when sedation was discontinued. These results support the use of cisatracurium as a suitable neuromuscular blocking agent for fast-track cardiac surgery.

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Early tracheal extubation in cardiac surgical patients reduces total cost and length of stay in the intensive care unit (ICU) without increasing the incidence of postoperative cardiorespiratory complications.[1] Nevertheless, this procedure required a change in anaesthetic practice. Using a long-acting neuromuscular blocking agent such as pancuronium, Von Oldenbeek and colleagues[2] reported that 65% of patients had inadequate neuromuscular function when sedation was stopped after cardiac surgery. Recently, cisatracurium besylate, a non-depolarizing neuromuscular blocking drug with an intermediate duration of action, has been recommended for use in cardiac surgery because it has no significant cardiovascular side-effects.[3] As the number of elderly patients requiring cardiac surgery increases, it is appropriate to use a neuromuscular blocking drug with pharmacodynamic and pharmacokinetic properties which are minimally affected by advancing age.[4] Limited data are available about the use of cisatracurium besylate during fast-track cardiac anaesthesia. The aims of this study were to investigate spontaneous recovery from cisatracurium-induced neuromuscular block after cardiac surgery, and to evaluate its suitability for use in patients undergoing early tracheal extubation after cardiac surgery.

Methods and results

After obtaining written informed consent, 18 patients undergoing cardiac surgery with cardiopulmonary bypass were included in this prospective study. Patients were entered into a fast-track protocol with the intent of early extubation. We defined an extubation time greater than 10 h after arrival in the ICU as delayed extubation.[5] Upon arrival in the operating room, a venous catheter and an arterial catheter were inserted under local anaesthesia and routine monitoring (five lead-ECG, pulse oximeter, non-invasive arterial pressure) instituted. Anaesthesia was induced with etomidate 0.3 mg kg^{-1}, remifentanil 1 μg kg^{-1} min^{-1} and cisatracurium 0.15–0.3 mg kg^{-1}. Anaesthesia was maintained using isoflurane in oxygen/air and a continuous infusion of remifentanil 0.2–1.0 μg kg^{-1} min^{-1}. The rate of the cisatracurium infusion was adjusted according to the response to stimulation of the orbicularis oculi muscle. Two surface electrodes were placed 2–3 cm anterior to the ear lobe. The upper branch of the facial nerve was stimulated every 15 s using train of four (TOF) supramaximal stimulation (30 mA) and the evoked responses of the orbicularis oculi muscle were estimated visually. The presence of one twitch response of the TOF at the orbicularis oculi was considered to be an adequate level of paralysis during surgery. Isoflurane end-tidal concentration and remifentanil infusion rate were adjusted according to the haemodynamic state of each patient and left to the discretion of the anaesthetist. Normothermic cardiopulmonary bypass was used in all patients. Intra-operative core temperature was recorded from nasopharyngeal and rectal probes and maintained around 35°C by using the heat exchanger on the cardiopulmonary bypass machine. Myocardial protection was achieved with intermittent antegrade blood cardioplegia. Haematocrit was maintained above 20%. The mean perfusion pressure was maintained between 50 and 70 mm Hg using isoflurane, remifentanil or norepinephrine. Additional monitoring included an end-tidal capnograph, a pulmonary arterial catheter and transoesophageal echography. The cisatracurium infusion was stopped at sternal closure.

In the ICU, patients were mechanically ventilated. Sedation was maintained with propofol 2 mg kg^{-1} h^{-1} and morphine 20 μg kg^{-1} h^{-1}. Postoperative monitoring included five lead-ECG, pulse oximeter, and radial and pulmonary arterial pressures. Blood temperature was recorded by the thermistor of the pulmonary artery catheter. On arrival in ICU, neuromuscular block was evaluated by monitoring the TOF ratio using acceleromyography (TOF GUARD Organon Teknika, Turnhout-Belgium) at the adductor pollicis muscle. Supramaximal TOF stimulation (60 mA) was applied every 15 s over the ulnar nerve. The skin temperature of the thumb was monitored, and was always higher than 32°C. The ICU medical staff was blinded to the values of the TOF ratio. Only when all criteria for the discontinuation of the sedation were obtained, was the value of the TOF ratio revealed. The criteria for the discontinuation of sedation were: blood temperature higher than 37°C; haemodynamic stability; absence of significant bleeding; and absence of hypoxaemia. As previously reported,[6] a TOF ratio equal to 0.9 was considered to lack of residual paralysis. Thus, the sedation was also continued until the TOF ratio reached this value. No reversal agent was administrated during the perioperative period. Spontaneous recovery times of the TOF ratio are demonstrated in Fig. 1.

On arrival in the ICU, all patients showed residual neuromuscular block (Table 1). The mean time to obtain a TOF ratio greater than 0.9 was 102 min (range 74–144 min) after discontinuation of the cisatracurium infusion. Fifteen patients (83%) were successfully extubated during the first 8 h after stopping the cisatracurium infusion (mean 5 h 29 min; range between 2 h 48 min and 7 h 10 min). The mean time from arrival in ICU to extubation was 4 h 39 min (range between 2 h 00 min and 6 h 20 min). Only one patient showed residual neuromuscular block when discontinuation of sedation was proposed by the medical staff in the ICU (TOF ratio was 75%).

Comment

In our study, before stopping the sedation in ICU, complete recovery from cisatracurium-induced neuromuscular block (i.e. TOF ratio greater than 0.9) was achieved in all except one patient; the remainder were successfully extubated early. Thus, the use of this neuromuscular blocking agent is suitable for fast-track cardiac surgery. However, cardiac surgery was performed at normothermia in this study. As

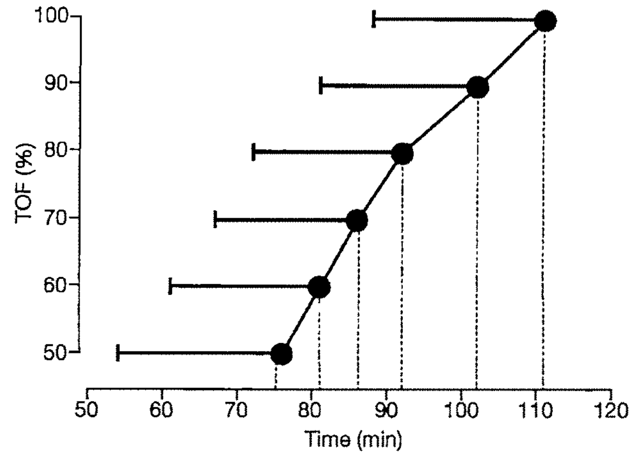

Fig 1 Spontaneous recovery profile of the TOF ratio from neuromuscular block after the end of the cisatracurium infusion. Data are means and horizontal error bars represent SD.

Table 1 Physical characteristics, and anaesthetic and surgical details. Results are expressed as mean (range)

Number of patients	18
Sex (M/F)	15/3
Age (yr)	68 (41–82)
Height (cm)	167 (151–176)
Weight (kg)	72 (55–95)
Duration of surgery (min)	206 (150–240)
Cardiopulmonary bypass time (min)	97 (62–142)
Cross-clamp time (min)	67 (33–105)
Lowest intraoperative temperature (°C)	35.1 (34.2–36.4)
Bolus dose of cisatracurium (mg kg^{-1})	0.22 (0.15–0.30)
Rate of cisatracurium infusion (µg kg^{-1} min^{-1})	2.3 (1.1–3.2)
Duration of cisatracurium infusion (min)	239 (191–375)
Blood temperature on arrival in ICU (°C)	36.4 (35.3–37.5)
pH on arrival in ICU	7.41 (7.31–7.50)
TOF ratio on arrival in ICU (%)	41 (19–70)

Hofmann elimination is temperature-dependent, our results may be reproducible only during normothermic cardiopulmonary bypass. A TOF ratio greater than 0.9 was used to avoid residual paralysis, as recently recommended.[6] Despite the rapid recovery (mean 102 min), the profile showed large interindividual variability (range between 74 and 144 min), as previously observed when cisatracurium was infused in non-cardiac surgery patients.[7] In that study, the recovery time from 5% twitch height to a TOF ratio greater than 0.7 ranged between 22 and 51 min.[7] This finding confirms that quantitative neuromuscular monitoring such as acceleromyography is necessary to avoid residual paralysis after cardiac surgery, even after a non-depolarizing neuromuscular blocking drug with an intermediate duration of action has been used. This problem has been raised by Von Oldenbeek.[2] Following pancuronium, the delay time from arrival in ICU to complete recovery ranged between 0 h 50 min and 8 h 15 min (mean 3 h 50 min). Additionally, their results were probably an underestimate because the value of the TOF ratio chosen as acceptable to avoid residual paralysis was 0.8 instead of 0.9 in our study.

Von Oldenbeck also reported that 13 of the 20 patients receiving pancuronium demonstrated a considerable degree of residual paralysis (median TOF 0.23) at the time sedation could be stopped.[2] In our study, only one subject showed residual neuromuscular block when the ICU medical staff decided to stop sedation. The TOF ratio of this patient was 75% and reached 90%, 20 min later. The majority of our patients (83%) were extubated early. Despite the small number of patients included in our study, the frequency of early extubation was similar to previous studies (82%).[1] Our results showed a long interval (mean 4 h 02 min; range between 1 h 56 min and 5 h 11 min) between return to adequate neuromuscular function and extubation. This delay confirms that recovery from paralysis is not the sole criterion for discontinuation of sedation after cardiac surgery.[5]

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BJA

CASE REPORTS

Successful epidural anaesthesia for Caesarean section in a patient with spondyloepiphyseal dysplasia

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Spondyloepiphyseal dysplasia congenita is a rare genetic entity in which it is very important to involve anaesthetists early on to discuss the possible anaesthetic complications for both general or regional anaesthesia. A case is described of a patient with spondyloepiphyseal dysplasia and multifetal pregnancy in which successful epidural anaesthesia for caesarean section was performed.

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Spondyloepiphyseal dysplasia congenita (SDC) is a rare entity characterized by pathological changes in the vertebral column and the epiphyses of long bones, which results in dwarfism.[1] Its precise incidence is unknown, but may be 1–2 per million.[2] In pregnant patients with SDC, Caesarean section is indicated because of the small pelvis. Early discussion with anaesthetists is very important because of the possible anaesthetic complications of both general and regional anaesthesia in such patients.[3–5] Only one case has been reported in the English literature on anaesthetic management in a pregnant patient with SDC, but none in patients with SDC and multifetal pregnancy.[5] The present report describes a case of a patient with SDC and multifetal pregnancy in which succesful epidural anaesthesia for Caesarean section was performed.

Case report

A 39 yr old nulliparous patient with SDC was admitted for elective Caesarean section. The patient's medical history revealed SDC diagnosed in late childhood. The patient had been wheelchair dependent since her 25th year as a result of bilateral hip dislocation. In another hospital, she had undergone an *in vitro* fertilization procedure because of idiopathic infertility; this resulted in a twin pregnancy.

Physical examination showed that the patient had a short trunk with a reduced xiphoid-to-pubic distance, marked lumbar kyphoscoliosis and shortened limbs. Her height was 134 cm and her weight 75 kg. Extension of the neck was normal, as were jaw movements. No neurological symptoms were found. Lung function test results were as follows (normal values in brackets): vital capacity, 2.40 litres (3.40 litres); total lung capacity, 3.45 litres (4.97 litres); functional residual capacity, 1.00 litre (1.60 litres); forced expiratory volume in 1 s, 2.10 litres (2.90 litres), showing a mild restrictive defect. Radiographic examination revealed severe lumbar kyphoscoliosis, flattening of the vertebral bodies at all levels and an inadequate pelvic outlet. However, x-rays of the cervical spine were normal.

As a result of these findings, Caesarean section was indicated, so preoperative consultation with an anaesthetist was performed early, at 14 weeks' gestation. Repeat lung function tests showed no further deterioration of the restrictive function, so Caesarean section was delayed until 37 weeks' gestation. Caesarean section under epidural anaesthesia was planned. Premedication was with ranitidine 150 mg orally on the night before and on the morning of the operation. Standard procedures, including non-invasive automatic monitoring of arterial pressure, oxygen saturation and electrocardiography, were used for monitoring the patient in theatre. Before surgery, a 1500 ml preload of Ringer's solution was administered. As a result of the lumbar kyphoscoliosis, the most comfortable position for the patient during epidural puncture was lying on her left

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side. After extensive palpation, an intervertebral space was found, which was considered to be the interspace L3–L4. After infiltration with local anaesthetic, a standard 18-gauge Tuohy needle was introduced, using the loss of resistance to air technique. The epidural space was identified 3 cm from the skin and a catheter was inserted 4 cm into the extradural space. After a test dose of 3 ml of 0.5% bupivacaine with 1:200 000 epinephrine showed no symptoms of subarachnoid or intravascular injection, 5 ml of 0.5% bupivacaine with epinephrine was injected. After 20 min, the upper level of sensory block, tested by pin-prick in the mid axillary line, was T5. The patient was turned supine with left lateral tilt. Mild hypotension was treated with intravenous ephedrine. Surgery proceeded uneventfully. The first child was a 2.7 kg male infant (Apgar scores 6 and 9) and the second a 2.8 kg female infant (Apgar scores 6 and 9). Oxytocin 5 IU was given at delivery. Postoperatively the epidural catheter was removed because of the unusual vertebral column anatomy of the patient. Total blood loss was estimated as 1500 ml. After anaesthesia, the course was uneventful and postoperative pain management was achieved with patient-controlled analgesia. Mother and children were discharged 5 days after delivery.

Discussion

SDC is a rare entity, which arises spontaneously or from X-linked or autosomal dominant inheritance.[1] The diagnosis is made at birth or in late childhood. SDC is characterized by pathological changes in the vertebral column, resulting in progressive kyphoscoliosis, platyspondyly, central anterior pointing of the vertebral bodies and atlantoaxial instability.[1 3–5] Laryngotracheal stenosis has also been reported in patients with SDC.[3] Kyphoscoliosis can impair respiration; in pregnant patients, this, combined with diaphragmatic splinting from the gravid uterus, may lead to severe respiratory problems. Our patient had marked lumbar kyphoscoliosis and was carrying more than one fetus, but only mild restrictive function disturbances were found.

At 14 weeks' gestation, advice was sought regarding potential problems with anaesthesia in this patient, including the possibility of laryngotracheal stenosis and a high risk of aspiration resulting from a combination of skeletal anomalies and compromised respiratory status. The decision was made to perform epidural anaesthesia. We also considered that, in case of accidental dural puncture, the Caesarean section would be performed under continuous spinal anaesthesia using a spinal catheter. A continuous regional technique was preferred to a 'single-shot' technique because of the anatomical abnormalities of the vertebral column and the unpredictable spread of local anaesthetic.[5] In our patient, the epidural space was entered with no problem. An appropriate sensory block was achieved with a low volume of local anaesthetic. The epidural catheter was removed because the unusual vertebral column anatomy increased the risk of unpredictable spread of local anaesthetics by continuous infusion.

In summary, we describe a case of a patient with SDC and multifetal pregnancy in which succesful epidural anaesthesia for Caesarean section was performed. The importance of early anaesthetic involvement in such patients is stressed.

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Use of remifentanil in a patient with peripartum cardiomyopathy requiring Caesarean section

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We describe a case of a 26 yr old primigravida at 39 weeks' gestation, with a diagnosis of peripartum cardiomyopathy, requiring urgent Caesarean section. The patient presented in severe heart failure and active labour. A general anaesthetic, using a target-controlled infusion of propofol and an intravenous infusion of remifentanil, was used to provide stable anaesthesia and analgesia for a successful delivery. The unusual diagnosis of peripartum cardiomyopathy and the potential benefits of the use of remifentanil in high-risk obstetric surgery are discussed.

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Peripartum cardiomyopathy is an uncommon cause of cardiac failure in obstetric patients. The management of such patients requires assessment of cardiac status and careful planning for the provision of safe analgesia and/or anaesthesia for delivery. Remifentanil is increasingly used as an anaesthetic agent providing cardiovascular stability in high-risk patients.[1] We report the management of a patient presenting in active labour with congestive cardiac failure due to peripartum cardiomyopathy and describe the successful use of remifentanil and propofol in the anaesthetic technique for her subsequent Caesarean section.

Case report

A previously well 26 yr old, 70 kg primigravida presented in labour for urgent Caesarean section at 39+6 weeks' gestation, complaining of mild shortness of breath, nausea, vomiting and increasing tiredness over the previous 2 weeks. On examination, she was dyspnoeic, with a pulse rate of 130 beats min^{-1} and arterial pressure of 90/60 mm Hg and had fine inspiratory crepitations in the mid-zones on chest auscultation. Initial management consisted of routine monitoring of maternal pulse, arterial pressure, oxygen saturation and temperature as well as fetal observations, with oxygen (35%) administered via a face mask. As symptoms were mild at this time, no further intervention other than close observation was undertaken and no firm diagnosis was made.

Over the next few hours, the patient's shortness of breath became worse and she developed a dry cough. An electrocardiogram (ECG) revealed left bundle branch block (LBBB) and a transthoracic echocardiogram demonstrated a markedly dilated left ventricle with an end-systolic diameter of 68 mm (normal=18–40 mm), global left ventricular dysfunction with an ejection fraction of 15%, mild functional mitral regurgitation and an enlarged left atrium. A chest x-ray showed cardiomegaly and signs of pulmonary oedema.

In view of the acute onset of symptoms over only a 2 week period with no previous history of heart disease and the echocardiographic findings of impaired left ventricular function without evidence of right ventricular strain, an initial diagnosis of peripartum cardiomyopathy with heart failure was made. It was felt unlikely that embolic disease or pre-existing heart disease was an aetiological factor in her deterioration. The patient was transferred to the regional cardiology unit (30 h after initial admission) for management of her congestive cardiac failure. Here, initial treatment consisted of oxygen, diuretics and digoxin as well as infusions of glyceryl trinitrate, dopamine and hydralazine. However, shortly after transfer, the patient began to experience contractions and vaginal examination showed that her cervix was 2 cm dilated. Early active labour was diagnosed and the patient was commenced on oral ranitidine 150 mg every 8 h.

Both the cardiac and obstetric anaesthetic on-call teams were contacted. A multidisciplinary decision was made that urgent Caesarean section under general anaesthetic would be the most appropriate method of delivery in view of the patient's haemodynamic status. Continuous fetal cardiotocograph monitoring demonstrated no fetal distress.

Preoperative monitoring was instituted, including invasive monitoring of arterial pressure via a radial arterial cannula, as well as measurement of pulmonary artery pressures, continuous cardiac output, mixed venous saturation and central venous pressure (CVP) via a pulmonary artery flotation catheter (PAFC). During PAFC placement, the patient developed complete heart block with a ventricular rate of 70 beats min^{-1}. This change in heart rhythm did not significantly alter the patient's haemodynamic parameters or symptoms. The PAFC was removed and several attempts at transvenous pacing were made unsuccessfully. The patient spontaneously reverted to sinus tachycardia with LBBB within 3–5 min. Before PAFC removal, right ventricular pressures of 50/16 mm Hg and pulmonary artery pressures of 48/24 mm Hg were recorded.

After oral administration of 30 ml of 0.3 M sodium citrate for antacid prophylaxis, preoxygenation and application of cricoid pressure, anaesthesia was induced in a semi-erect position using a target-controlled infusion (TCI) of propofol (target blood concentration 1.5 $\mu\text{g ml}^{-1}$), and an infusion of remifentanil at 2 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$. Rocuronium 70 mg was administered after loss of verbal response to achieve muscle relaxation. The patient was intubated 90 s later with a 7.5 mm internal diameter endotracheal tube following grade 1 view on laryngoscopy.

Maintenance of anaesthesia was achieved by continuation of the TCI propofol (target plasma concentration range 1.0–2.5 $\mu\text{g ml}^{-1}$) and remifentanil infusions. After 5 min the remifentanil infusion rate was reduced to 1.2 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$ for 28 min before being reduced again to 0.8 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$. The patient was ventilated with an air/oxygen mixture ($F\text{I}_{\text{O}_2}$ 0.5). Once the airway had been secured, a transoesophageal echocardiography (TOE) probe was passed in order to assess valvular and chamber function. There was no significant change from the preoperative transthoracic echocardiogram findings, revealing a dilated left atrium and ventricle in association with poor left ventricular systolic function and moderate mitral regurgitation.

During the perioperative period, the patient remained haemodynamically stable, her heart rate varying between 120 and 140 beats min^{-1} and her systolic and diastolic arterial pressures varying between 120 and 140 and between 57 and 80 mm Hg, respectively. Infusions of glyceryl trinitrate (0.7 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$) and dopamine (10 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$) were continued intraoperatively. A live female infant was delivered 8 min after induction of anaesthesia with Apgar scores of 6 and 8 at 1 and 5 min, respectively, and received intramuscular naloxone (20 μg). Oxytocin was administered by slow intravenous infusion following manual massage of the uterus. The patient demonstrated remarkable haemodynamic stability during delivery and for the remainder of the case.

Postoperatively, the patient was transferred to the cardiac intensive care unit, still intubated, for continuous haemodynamic monitoring. Sedation was continued with an intravenous propofol infusion and a remifentanil infusion at 0.8 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$ to maintain a Ramsay sedation score of 3. A morphine infusion at 3 mg h^{-1} was also commenced on return to the intensive care unit. The remifentanil infusion was discontinued after 3 h and the patient was extubated uneventfully 2 h later when all sedation had been weaned. Due to the high risk of thromboembolism, prophylaxis with the low molecular weight heparin enoxaparin (40 mg subcutaneously every 24 h) was commenced. After a period of observation the patient was returned to the cardiology high dependency unit. Her subsequent post-operative course was uncomplicated.

Further investigations carried out before discharge 2 weeks later included a myocardial biopsy revealing a non-specific inflammatory picture and echocardiography which demonstrated no improvement in ventricular function. When reviewed at 6 months, the patient felt symptomatically much improved but continued to have a reduced exercise tolerance and on echocardiographic examination showed global impairment of left ventricular function associated with moderate mitral regurgitation and a calculated left ventricular ejection fraction of 16%. The female infant remained healthy.

Discussion

Peripartum cardiomyopathy is a rare congestive cardiomyopathy of unknown aetiology which is associated with extremely high mortality.[2] It was first described as a separate entity in the 1930s, distinguishing it from other causes of heart failure associated with pregnancy due to ischaemic, valvular, metabolic or infective aetiologies. It has several established diagnostic criteria including:[2] (i) development of cardiac failure in the last month of pregnancy or within 5 months after delivery; (ii) absence of a determinable cause for cardiac failure; (iii) absence of demonstrable heart disease before the last month of pregnancy; and (iv) echocardiographically demonstrable impairment of left ventricular function. Other clinical conditions, which may mimic heart failure, such as amniotic and pulmonary emboli, should be excluded when considering the diagnosis.

Our patient presented at 39+6 weeks' gestation describing a 2 week history of increasing shortness of breath. Before this presentation she was in good health with no suggestion of previous cardiac disease. Cardiotocograph and fetal assessment were unremarkable and there was no suggestion of pre-eclampsia or other obstetric aetiology for her deteriorating condition.

The delay in our patient's diagnosis after initial presentation may reflect the rarity of this condition. Incidence is reported to range from one in 1300 to one in 15 000 pregnancies.[3] Peripartum cardiomyopathy is thought to be more prevalent in women over 30 years of age, multiparous women, those of African descent[2 3] and in women receiving tocolytic therapy. Other possible risk factors including toxaemia of pregnancy,[4] cocaine abuse[5] and nutritional deficiencies[6] have also been reported. The aetiology of peripartum cardiomyopathy is not known, raising the question that it may not in fact be a separate entity.

Various theories include hormonal and immunological imbalance as well as myocarditis[7] as possible aetiological factors, but to date no study has been conclusive in this regard.

Our patient presented with symptoms that made initial diagnosis of this condition difficult. The symptoms of fatigue, cough, dyspnoea and abdominal pain are characteristic of peripartum cardiomyopathy but also of many of the differential diagnoses. Our diagnosis was one of exclusion based on the absence of any previous history of cardiac disease in a young, normally healthy female presenting acutely in the last month of pregnancy in association with the absence of clinical or echocardiographic findings suggestive of embolic disease. As our patient was already in active labour and beginning to experience discomfort associated with uterine contractions, we were faced with the dilemma of deciding which method of delivery and which forms of anaesthesia and analgesia were most appropriate. In view of the patient's haemodynamic status and the possible effects of a vaginal delivery on her systemic vascular resistance (SVR) and cardiac workload, it was decided that a Caesarean section would be the safest method of delivery.

With a recorded ejection fraction of 15% and the possible effects of haemodynamic compromise associated with sympathetic blockade, a general anaesthesia technique was felt to be the best method of providing stable analgesia and anaesthesia for delivery. Regional anaesthesia may have provided an advantageous reduction in afterload but its effects on haemodynamic status were felt to be less predictable than that of a general anaesthetic using suitable agents.

Remifentanil, a synthetic opioid, has several distinctive pharmacokinetic properties, which include a unique metabolism by plasma and tissue esterases and a context-sensitive half-life of 3–4 min, independent of the duration of infusion.[8] Remifentanil's opioid properties allow control of the intraoperative stress response and allow a more rapid recovery than other commonly used opioids. As our patient had significant haemodynamic instability, we felt that remifentanil could provide us with an agent which could significantly reduce the stress response and subsequent possible detrimental effect on SVR. The dose regimen chosen for the propofol and remifentanil infusions were based on the authors' experience and practice in patients undergoing cardiac surgery.

The transfer of conventional opioids across the placenta may risk resultant neonatal depression. The use of remifentanil would, in theory, through its metabolism and short duration of action, avoid this problem. Data on the pharmacokinetics of remifentanil in the neonate suggest a similar pattern of metabolism to older children and adults.[9 10]

In this case the infant was born with Apgar scores of 6 and 8 at 1 and 5 min, respectively. The decision to administer naloxone was taken by the paediatrician in attendance, who before the start of the procedure had been informed of the nature of the anaesthetic agents to be given. It is our opinion that the use of remifentanil minimized CNS and respiratory depression in the infant, a feeling supported by the experience of others.[11]

The decision to insert a PAFC in the presence of LBBB may be controversial in view of the risk of inducing complete heart block, but was taken as it was felt that the information obtained, such as pulmonary capillary wedge pressure and cardiac output, with the ability to derive parameters such as stroke volume and SVR, would be very helpful in the perioperative management of the patient. Various arrhythmias have been described during cardiac catheterization, but as the right bundle branch lies below the tricuspid valve, a pulmonary artery catheter may interfere with the normal conduction and result, as in our case, in complete heart block in those patients with pre-existing LBBB.[12 13]

Treatment of peripartum cardiomyopathy follows the same principles as that for other causes of cardiac failure, including diuretics, inotropic support, vasodilators and, more controversially, angiotensin-converting-enzyme inhibitors.[2] Thromboembolic complications are not uncommon and the use of anticoagulants is often recommended.[14]

The use of immunosuppressives is controversial in that the vast majority of patients, like our patient, show only non-specific inflammatory changes on myocardial biopsy. However, cardiac transplantation has been successful in some patients.[2] The mortality rate in the USA has been reported to range from 25% to 50%, the majority of deaths occurring within 3 months after delivery as a result of either progression of cardiac failure or sudden death associated with arrhythmias or thromboembolic phenomenon.[2 15] Data on recovery of myocardial function, assessed by both symptoms and echocardiography, suggest that some patients who survive will continue to have impaired cardiac function. The recurrence of peripartum cardiomyopathy in a further pregnancy in a patient previously diagnosed with the condition, whether or not cardiac function has recovered, is widely reported and most experts would discourage future conception in view of the extremely high risk of increased morbidity and mortality associated with both gestation and delivery.[16 17]

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Reduction of vasopressor requirement by hydrocortisone administration in a patient with cerebral vasospasm

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A 67-yr-old female received hypertensive, hypervolaemic treatment for cerebral vasospasm after severe subarachnoid haemorrhage. After 3 days of continuous vasopressor infusion and despite adequate hydration and normal cardiac function, the phenylephrine dose had to be increased to obtain the same systolic blood pressure. This tachyphylaxis to phenylephrine infusion was probably caused by down-regulation of α adrenoceptors, and was reversed by giving i.v. hydrocortisone.

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Vasoactive drugs are used to induce hypertension in patients with subarachnoid haemorrhage (SAH) who develop cerebral vasospasm and are being treated with triple-H therapy (hypertension, hypervolaemia and haemodilution).[1] This treatment is often needed for up to 2 weeks, beyond which time clinical vasospasm is rarely observed.[2] Prolonged administration of adrenoceptor agonists has been associated with decreased adrenoreceptor density,[3 4] which may increase the need for these drugs to achieve the same induced hypertension.[5] In this report, hydrocortisone reversed the increased dose requirement for phenylephrine in a patient with cerebral vasospasm. This is the first report of the use of hydrocortisone for tachyphylaxis.

Case history

A 67-yr-old otherwise healthy woman presented with Hunt and Hess' grade 4 SAH[6] (World Federation of Neurosurgical Surgeons grade 5 haemorrhage) and was immediately admitted to the intensive care unit (ICU) for

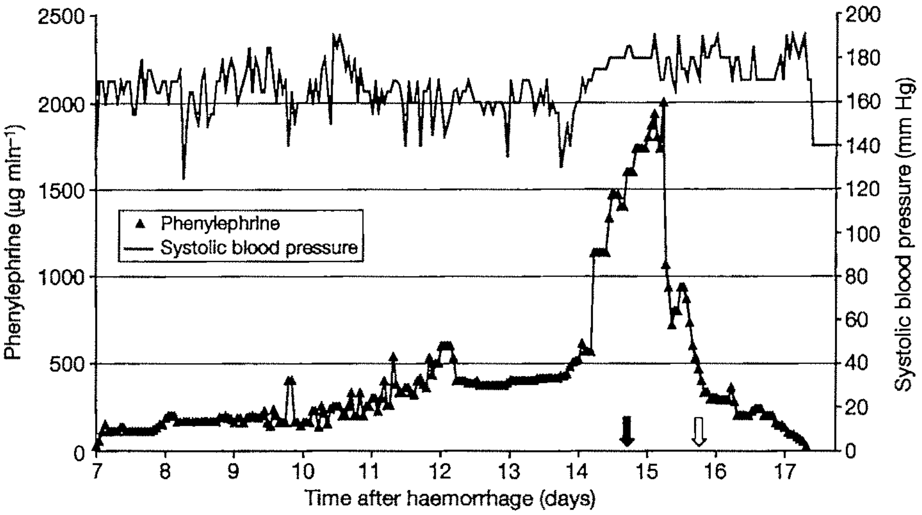

Fig 1 Changes in phenylephrine requirement and systolic arterial pressure. The solid and open arrows represent the first and last doses of hydrocortisone respectively.

management (day 0 after SAH). Her heart rate was 110 min^{-1}, arterial pressure 120/75 mm Hg, and Glasgow Coma Scale score 6. The trachea was intubated and mechanical ventilation with pressure support of 10 cm H_2O, PEEP (positive end-expiratory pressure) of 5 cm H_2O and FI_{O_2} of 0.40 was started. Computed tomography (CT) scanning of her brain showed blood in the basal cisterns, sulci, sylvian fissure, anterior falx and the lateral ventricles, but there was no evidence of hydrocephalus. Arterial and central venous catheters were inserted for invasive pressure monitoring, and the patient was given normal saline. Several hours after her presentation and admission to the ICU, the patient was opening her eyes to voice and following commands with her right side but had left hemiparesis. She was not hyperventilated and her arterial blood gases were normal throughout the course of her ICU stay. One day after the SAH, a cerebral angiogram showed anterior communicating and left posterior communicating artery aneurysms without evidence of cerebral vessels narrowing. She was given oral nimodipine 60 mg every 4 h. Four days later coils were placed in both aneurysms. The patient's neurological state did not change. On day 6, a baseline transcranial Doppler (TCD) examination showed no cerebral vasospasm, with a mean flow velocity in the middle cerebral arteries (MCA) of 110 cm s^{-1}. On day 7, the patient's level of consciousness decreased despite maintenance of normal arterial pressure (130/80 mm Hg), adequate urine output (>0.5 ml kg^{-1} h^{-1}) and satisfactory central venous pressure (CVP) of 10 mm Hg. She could localize stimuli with her right upper arm and withdrew her right leg on stimulation. A repeat TCD examination showed that mean flow velocity had increased to 139 cm s^{-1} in the left MCA. Phenylephrine infusion was started at 100 μg min^{-1} to maintain systolic blood pressure (SBP) at 170–190 mm Hg. The neurological state rapidly improved after the target SBP was achieved with the phenylephrine infusion. In addition to the hypertensive therapy, i.v. hydration with normal saline and intermittent doses of pentastarch were given to keep the CVP ≥12 mm Hg. A pulmonary artery catheter was inserted. The cardiac index was 4.11 litre min^{-1} m^{-2}, pulmonary artery occlusion pressure (PAOP) 15 mm Hg, and CVP 15 mm Hg. A repeat cerebral angiogram on the 8th day after SAH showed minimal left MCA vasospasm, although a quantitative measure of the vessel diameter was not available. Nevertheless, the triple-H therapy was continued because of the clinical evidence of continuing cerebral vasospasm.

Despite the maintenance of adequate hydration (CVP and PAOP ≥12 mm Hg) and the presence of normal cardiac function (cardiac index ≥4.0 litre min^{-1} m^{-2}), the phenylephrine dose had to be increased 3 days after starting the vasopressor therapy to maintain the same initial target SBP of 170–190 mm Hg. There was no clinical or laboratory evidence of infection, renal dysfunction or acid–base disturbance at any time. The patient continued to have clinical evidence of cerebral vasospasm as her conscious state consistently deteriorated and then rapidly returned to normal whenever her SBP decreased below 170 mm Hg and was then restored. These transient episodes of relative hypotension occurred in relation to medication bag replacement and after nimodipine administration. The nimodipine dose was halved and then discontinued because hypotension occurred after each dose of nimodipine. On day 14 after SAH, a morning serum cortisol sample was taken and hydrocortisone 100 mg i.v. every 8 h was started, with a consequent reduction in phenylephrine infusion rate from a maximum of 2000 μg min^{-1} to 800 μg min^{-1}. This decrease in vasopressor requirement occurred after three doses of hydrocortisone and without changing the target SBP (Fig. 1). The serum cortisol concentration was 566 nmol litre^{-1} (normal range 119–618 nmol litre^{-1}) and the patient maintained normal acid–base and renal function.

Phenylephrine dose requirement continued to decline to 50–100 µg min^{-1}, to give an SBP of 170–190 mm Hg. After five doses, hydrocortisone was discontinued without any increase in phenylephrine dose requirement or any change in the target SBP. On day 17 after the SAH, the phenylephrine infusion rate was gradually decreased and then stopped. The SBP returned to 140 mm Hg without any change in the patient's condition. On day 18 after the SAH, the patient was discharged from the ICU, with persistent left hemiparesis.

Discussion

Adrenoceptor agonists such as phenylephrine and norepinephrine are used to cause hypertension in patients with cerebral vasospasm after SAH. These drugs are usually given for up 2 weeks after the onset of vasospasm, which can decrease responsiveness to these vasoactive agents. In animal studies, adrenoceptor down-regulation and decreased responsiveness occur when catecholamines are given in large doses and/or for long periods.[7–9] Similar findings occur in human subjects.[10–12] In this report, phenylephrine was infused for three days before a progressive increase in dose requirement, to achieve the same target blood pressure, was observed (Fig.1). The haemodynamic values measured by the pulmonary artery catheter indicated that adequate hydration and normal cardiac function were maintained. Down-regulation of α adrenoceptors is the likely explanation for the observed increase in phenylephrine dose requirement. Although previous reports have documented β receptor down-regulation in relation to prolonged exposure to β agonists,[7–12] the findings of this report suggest that selective down-regulation may also involve α adrenoceptors. This has not been reported previously.

Although receptor reappearance has been described after stopping the adrenoceptor agonist,[13] withholding phenylephrine was not possible in this patient because of persistent cerebral vasospasm, shown by the reproducible deterioration in the patient's level of consciousness whenever her SBP decreased below 170 mm Hg, during medication bag replacement and after nimodipine administration. Halving the dose of nimodipine did not affect the decrease in SBP, with a concomitant deterioration in the patient's level of consciousness after the administration of each dose of the drug. Corticosteroids prevent homologous down-regulation of β_2 receptors[14] and up-regulate lymphocyte β receptors.[15 16] In addition, Aziz *et al.*[17] have reported that inhaled budesonide resensitizes the cardiac β_2 receptor response to salbutamol in patients treated with long-acting β_2 agonists. Bollaert *et al.*[18] described an improvement in the haemodynamic profile of patients with late septic shock who were treated with hydrocortisone in the absence of adrenal insufficiency. In this case report, vasopressor requirements were reduced by 50% within 12 h of hydrocortisone administration (Fig. 1), with no change in the patient's CVP, PAOP or cardiac index, and with no clinical or laboratory evidence of adrenal insufficiency, acid–base disorder or renal dysfunction. On the basis of the study of Bollaert *et al.*[18] and because the phenylephrine dose requirement decreased to a reasonable level of 50–100 µg min^{-1}, hydrocortisone was stopped after five doses of the drug.

Although steroid-induced up-regulation of the α adrenoceptors is one possible explanation for the decrease in phenylephrine requirement, another potentially plausible explanation is steroid-induced inhibition of nitric oxide synthase (NOS). Inhibition of this enzyme decreases endogenous production of nitric oxide (NO), a potent vasodilator that has been implicated in vascular hyporeactivity. This potential mechanism is supported by the findings of Szabo *et al.*,[19] who found that NO-induced vascular hyporeactivity was reduced after dexamethasone, an NOS inhibitor. Similar findings were observed by Thiemermann and colleagues in rats with haemorrhagic shock.[20] Whether the administration of large doses of phenylephrine induces the enzyme NOS is an intriguing question, but steroid-induced NOS inhibition has been shown only in animals. Future human studies are needed.

In conclusion, this case report demonstrated that short-term i.v. hydrocortisone decreased the escalating phenylephrine dose requirements in a patient with SAH who was being treated with induced hypertension to counteract cerebral vasospasm. Although α adrenoceptor up-regulation in response to steroid therapy is a plausible explanation, the exact mechanism of the steroid-induced reduction in vasopressor requirement remains undetermined. Studies on the effect of steroids on vascular hyporeactivity in response to prolonged administration of an adrenoceptor agonist are warranted.

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British Journal of Anaesthesia **86** (1): 141–2 (2001)

Paradoxical changes in bispectral index during nitrous oxide administration

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I report two patients undergoing open heart surgery, with nitrous oxide and isoflurane anaesthesia, for whom bispectral index (BIS) monitoring showed high BIS values with nitrous oxide and isoflurane anaesthesia. The BIS decreased immediately after nitrous oxide was stopped and increased again after nitrous oxide was restarted.

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Key words: monitoring, bispectral index, depth of anaesthesia

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The bispectral index (BIS) is a variable, derived from the EEG, that has been reported to have the ability to measure the hypnotic component of the anaesthetic state and has been shown to correlate well with the degree of sedation using several general anaesthetics.[1 2] I have been using BIS monitoring (Aspect A-1000 EEG monitor; Aspect Medical System Inc., MA, USA) to titrate anaesthesia in cardiac surgery patients for the last 3 years. During this period, I found two patients (out of more than 300) in whom increasing the concentration of potent inhalational anaesthetic was associated with no change in BIS. Instead, the BIS decreased upon discontinuation of nitrous oxide and increased again after the reintroduction of nitrous oxide.

Case reports

Case 1

A 35 yr old woman was scheduled for mitral valve replacement for mitral regurgitation. Anaesthesia was induced with morphine 0.2 mg kg^{-1} and midazolam 0.1 mg kg^{-1} and a titrated sleep dose of thiopental. The BIS was monitored using silver chloride electrodes applied to the forehead, with one on each malar bone, one at the centre of the forehead and a ground electrode on one side of the centre electrode. Tracheal intubation was facilitated with the use of vecuronium 0.1 mg kg^{-1} and the lungs were mechanically ventilated. Anaesthesia was maintained with 66% nitrous oxide in oxygen and with isoflurane. Ten minutes after tracheal intubation, the BIS increased to >90. It did not decrease even with increasing doses of isoflurane (inspired concentrations of ⩽3% isoflurane). At this point the patient's arterial pressure began to decrease. Nitrous oxide and isoflurane were stopped and the patient was given 100% oxygen. Two minutes after the nitrous oxide was discontinued, the BIS started to decrease; it fell to <30 after another 5 min. After a further 5 min, the systemic arterial pressure had improved. Nitrous oxide was then reintroduced, whereupon the BIS increased; the BIS fell again after the nitrous oxide was stopped. BIS monitoring was abandoned and anaesthesia controlled using clinical judgement.

Case 2

A 60 yr old man was scheduled for coronary revascularization. Anaesthesia was induced and maintained as in case 1. In spite of adequate concentrations of isoflurane (2–3% inspired concentrations), the BIS remained at >90. Nitrous oxide was stopped and the BIS decreased to <50 within 5 min. Reintroduction of nitrous oxide again increased the BIS.

Discussion

The ability of nitrous oxide to reduce the requirement for other anaesthetic agents has been well described.[3 4] Yamamura and colleagues[5] studied the effect of nitrous oxide on the EEG of healthy volunteers and showed an increase in high β-range activity after nitrous oxide administration. Rampil and colleagues[6] found that inhalation of nitrous oxide was associated with an increase in high-frequency and θ-range activity of the EEG but this did not alter BIS. A reduction in nitrous oxide concentration was associated with a sudden increase in high-amplitude δ activity of the EEG along with a decrease in BIS.[6] Nitrous oxide in combination with more potent anaesthetics has been studied previously. Porkkala and colleagues[7] have shown that nitrous oxide antagonizes the depressant effects of isoflurane on the EEG. Sebel and colleagues[8] found that the BIS was higher when isoflurane was used in combination with nitrous oxide than when it was used without nitrous oxide. Analogous effects were observed in a study by Glass and colleagues, who showed that the addition of nitrous oxide to propofol increased the BIS at which patients failed to respond to verbal commands.[2] Barr and colleagues found no effect of nitrous oxide on the BIS when given alone or added to isoflurane.[9] These conflicting reports of the effect of nitrous oxide on the BIS show that the effects of nitrous oxide are not consistent, reflecting a potential inadequacy of the algorithm used for calculating the BIS from the EEG.

The algorithm that computes the BIS evaluates predominantly three features of the EEG: the ratio of very high β-range activity to high α plus low β activity (relative β ratio), very high β-range phase relationships and burst suppression phenomena. These features are used sequentially by the algorithm as sedation and anaesthesia increases, with relative β ratio being the most influential feature during light sedation. As no single pattern of EEG reflects depth of anaesthesia correctly, a number of features are used to calculate the BIS. The paradoxical changes in the BIS of our patients may have resulted from an alteration in the relative β ratio with nitrous oxide or withdrawal of nitrous oxide. These findings question the utility of monitoring BIS in controlling the depth of anaesthesia in patients receiving nitrous oxide in addition to other anaesthetic agents. Other neurophysiological measures of depth of anaesthesia may be prone to similar problems with nitrous oxide.[7 10 11]

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Therapeutic embolization of an internal mammary artery damaged by placement of a central venous catheter

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We describe the embolization of a left internal mammary artery damaged by left internal jugular venous catheterization. Because potentially serious complications can occur with a blind approach for central venous catheterization, portable ultrasound machines should be used more often to ensure correct placement of the catheter.

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Keywords: complications, artery puncture

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Central venous catheters are used commonly in hospital practice for the administration of fluid, drugs and parenteral nutrition as well as for the measurement of central venous pressure to guide fluid balance. They can cause rare but potentially serious complications.[1–7] We describe a case in which inadvertent arterial puncture occurred during attempted left internal jugular catheter insertion via a skin puncture at the root of the neck. This damaged the internal mammary artery. Bleeding after removal of the catheter was treated successfully by microcatheter embolization.

A 22-yr-old primigravida was admitted to hospital at 41 weeks gestation with pre-eclampsia. Labour was induced by artificial rupture of the membranes and an epidural catheter was inserted. Labour failed to progress satisfactorily, and when meconium staining of the liquor was noted plans were made for emergency Caesarean section. A central venous catheter was inserted to monitor central venous pressure according to the local protocol for the management of pre-eclampsia.

A left jugular approach with a puncture at the root of the neck was used. A single-lumen 19 G catheter was inserted using the Seldinger technique and the procedure was described as straightforward. Blood was freely aspirated, and this was taken as evidence that the tip of the catheter was within the lumen of the vein. A water manometer was used to measure the central venous pressure, which was recorded as 0 mm of water.

The Caesarean section was completed uneventfully and a healthy child was delivered. After the operation the patient became tachycardic and oliguric. The chest X-ray (Fig. 1) taken 6 h later shows shadowing in the left lower and mid zones and an unusual course of the central cannula, but the importance of this was not appreciated at the time. The haemoglobin concentration was 73 g litre^{-1} and three units of blood were transfused.

The patient subsequently improved but the left basal shadowing persisted despite starting antibiotics. An ultrasound scan showed fluid rather than consolidation at the left base, and 1 litre of bloodstained fluid was aspirated from the left pleural cavity 3 days after delivery. The following day the left internal jugular catheter was removed. The patient immediately became hypotensive (systolic blood pressure 40 mm Hg) and collapsed. She was given i.v. fluids and a chest X-ray showed a large left-sided effusion with mediastinal shift to the right side. An intercostal chest drain was inserted and heavily bloodstained fluid was aspirated. A leaking vessel in the left side of the chest was suspected and the patient immediately underwent angiography to identify the source of bleeding. Selective left subclavian artery angiography using a 5F vertebral catheter from the groin demonstrated extravasation of contrast from the left internal mammary artery (Fig. 2). The left internal mammary artery (IMA) had been inadvertently punctured during the insertion of the central line and the line had been introduced alongside this vessel, which led to bleeding. Some leakage of arterial blood around the catheter had occurred whilst it was in place, but when the catheter was removed a potentially catastrophic bleed occurred.

A tracker 18 coaxial catheter (Target Fremont, California, USA) was used to catheterize the left IMA selectively. A 4 mm pretzel coil was placed in the IMA just distal to the laceration in order to 'close the back door'. This was followed by two further 4 mm coils, one at the site of laceration and one proximal to it, just beyond the origin of the IMA. As a supplementary measure, a small volume of 300–500 μm Ivalon particles was carefully injected in order

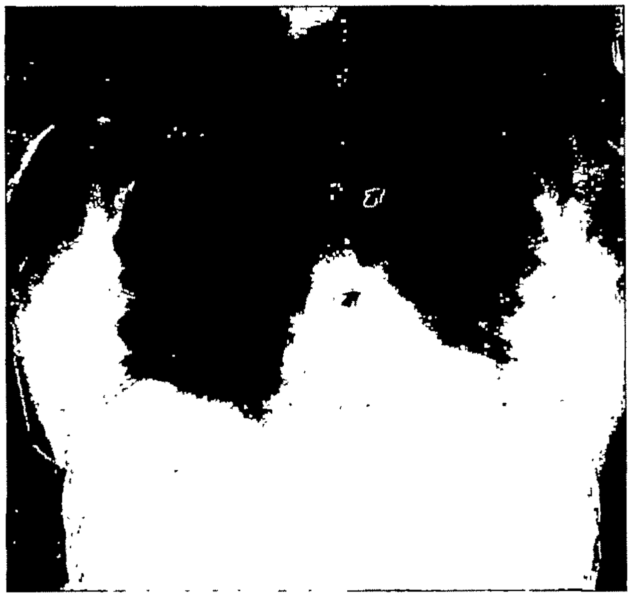

Fig 1 Chest x-ray showing left-sided central catheter with vertical orientation lying outside the left jugular and brachiocephalic veins (arrows) with the tip in the pleural space and a left-sided pleural effusion. Note the low access site within the neck.

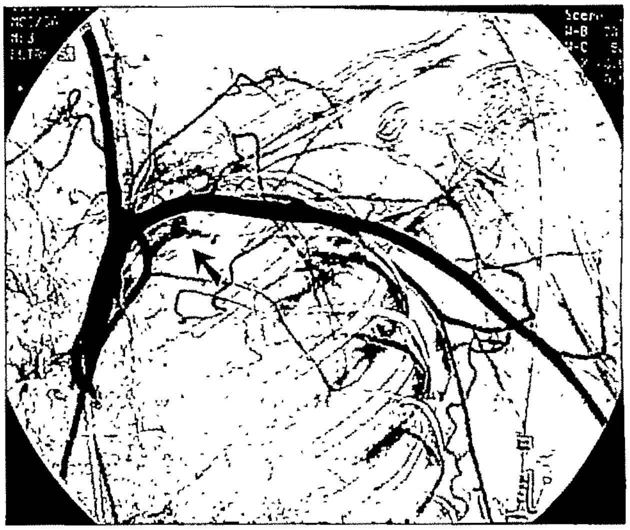

Fig 2 Selective left subclavian arteriogram showing haemorrhage (arrow) from a lacerated proximal left internal mammary artery.

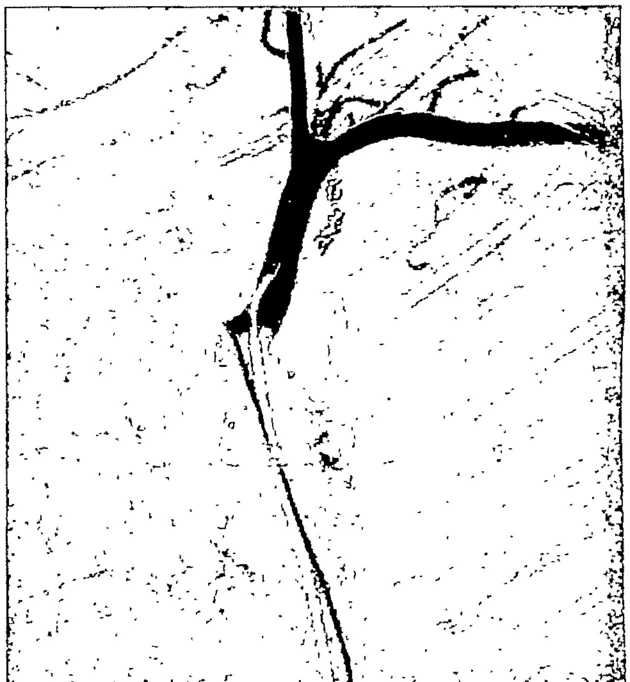

Fig 3 Selective left subclavian arteriogram showing complete occlusion of the left internal mammary artery with pretzel coils, with cessation of haemorrhage.

to promote rapid thrombosis within the coils. Check angiography after this procedure confirmed complete cessation of the leak (Fig. 3). The patient's pleural effusion persisted, with partial collapse of the left lung. The effusion was very loculated and resistant to aspiration, and eventually pleural decortication was done to allow re-expansion of the lung. The patient had no further bleeding and eventually made a full recovery.

Discussion

Complications of central venous catheterization are well described.[1–7] These include inadvertent arterial puncture, haematoma, thrombophlebitis, brachial plexus damage, thoracic duct puncture, mediastinal fluid infusion and pneumothorax.

Central venous catheters can be inserted via the internal jugular and subclavian veins. Complications are less frequent and severe after cannulation of the internal jugular vein compared with the subclavian vein.[8] Internal jugular vein cannulation can be classified as high or low, which refers to the needle's insertion in relation to the apex of the lung. A high approach is defined as a puncture at or above the apex of the triangle formed by the two heads of the sternocleidomastoid. As many as eleven different approaches to the internal jugular vein have been described.[9–19] The incidence of pneumothorax and arterial injury is generally greater with the low approach.

Ultrasound guidance when siting venous catheters reduces the incidence of complications, as does direct visualization of the puncture of the vein wall, as well as identifying diminutive or thrombosed vessels.[20] Some recommend that ultrasound guidance should be used for all central venous catheterization.[21 22]

In this case, misplacement of the jugular venous catheter could have been diagnosed on the initial chest x-ray after the procedure (Fig. 1). This shows that the central catheter does not conform to the path of the left jugular and brachiocephalic veins but pursues a more vertical course. Because blood was freely aspirated, the catheter was believed to be in the internal jugular vein. In fact, this blood was from the bleeding from the damaged IMA. The internal jugular catheter was passed intrapleurally and by chance reduced bleeding from the IMA. When the catheter was removed and a haemothorax developed, arterial damage was recognized.

The source of bleeding was well shown by selective angiography, and embolization was performed with a satisfactory result. The microcatheter system allowed selective catheterization and embolization of the IMA. The technique described illustrates the principle of 'closing the back door' before occluding the bleeding vessel to prevent back-bleeding from the distal vessel. The purpose of the Ivalon particles was to promote rapid thrombosis within the coils because of the brisk haemorrhage from the tear.

This is the first case we can identify in the literature in which damage to the IMA caused by low puncture of the neck during internal jugular venous catheterization has been treated successfully by microcatheter embolization.

In conclusion, venous or arterial haemorrhage should be considered in a shocked patient after central catheter removal. Small portable ultrasound machines are now available which allow guided access for all central venous catheterizations. Their use might reduce the incidence of complications and reduce the time taken for catheterization. Should a complication occur, angiography should be considered in order to locate the bleeding, and occasionally embolization may obviate the need for major surgery.

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Correspondence

Parenteral nutrition: down but not out!

Editor—I am concerned that the editorial on metabolic support in the critically ill[1] tried to sound the final bell for parenteral nutrition (PN) in intensive care. While I find this a worrying over-interpretation of the evidence, I realize their judgement is based upon a very poor meta-analysis of the application of parenteral nutrition.[2] In this collection of disparate studies they rightly remind us that in the review only 1 in 5 of the studies involved intensive care patients. These were individually valid studies in different specialist patient populations, but with less relevance when aggregated and applied to general intensive care. Meta-analysis correctly applied brings together a number of well-controlled, high quality studies in a distinct patient population and diagnosis to generalize a contribution made by a specific treatment. Since none of these features apply to the meta-analysis on parenteral nutrition why is it given such credence? Based upon such a poor foundation it is surprising that the authors feel able to state so confidently that there is no role for PN in the critically ill in the face of these 'unambiguous conclusions'.

It is right to question the correct application of PN in the critically ill as the issues are complex and determined by the assessment of gastrointestinal function. Remember that patients with complete gastrointestinal failure live full lives today because of total PN, and many studies attest to the utility of PN in the malnourished. Although, because the proof that PN improves outcome of ICU patients with temporary gastrointestinal failure has eluded us may well be a reason to use it wisely, it is no justification to discard it. We would have very few supportive therapies left in ICU if we took this approach! Are we going to deprive patients of oxygen even though there is little evidence that much of our struggle to correct hypoxia alters outcome?[3] Carrying the argument of the authors forward I would suggest that it be up to the intensive care community to show, based upon a background of sound metabolic research, that a worse outcome is *not* associated with depriving malnourished ICU patients suffering gastrointestinal failure of their only source of nutrition. However, such patients are in the minority and the overwhelming majority of patients can and should receive some enteral feed in ICU by a variety of routes. The more important question regarding PN provision is its use in the grey area when we are not sure whether the gut has failed or when there is partial failure of enteral feeding. Although we are ready to attribute the risks linked to parenteral nutrition, we appear slow to catch up with the list of morbidity and mortality risks associated with enteral feeding and that the failure rate is high.[4] How hard should we persist with enteral feeding before the risks outweigh the benefits? Does supplemental PN in this situation only add a new level of risk without any benefits?[5] Do we have the evidence that the current practice of sub-optimal enteral feeding is sufficient in the long term for all? I doubt it. The authors should examine the poor success of enteral feeding in the enteral immunonutrition studies they cite and the worse outcome of the less well-fed patients. Even among the proponents of enteral feeding in intensive care there is a realization that there is still a place for PN.[6]

I can agree with the authors that such nutrition questions ideally need to be answered by good, adequately powered collaborative studies in intensive care. Who will fund them in the UK? Commercial incentives only exist for new, costly products. The design is crucial if they are to succeed in answering the questions given the frequent failure of therapeutic studies in intensive care to link a specific treatment to a valid outcome. The Canadian collaborative groups are leading the way in delivering large powered clinical studies that may address these issues and provide the real evidence we need. Our knowledge regarding nutrition today is based upon several decades of metabolic research and nothing I have seen suggest that 'TPN in the critically ill is of historical interest only'.

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Editor—Nutritional support of the critically ill patient is a subject that is often neglected, and informed discussion is to be welcomed. We were therefore dismayed by the negative perspective on immunonutrition taken by Kennedy and Hall[1] in their editorial, and believe that their conclusions should have been different. They emphasize the flaws in the meta-analysis of studies in patients with critical illness or cancer from Heys and colleagues,[2] particularly the possibility that an increased early mortality rate was the true cause for reduced infections and hospital stay seen in the immunonutrition group. They then misquote the study by Atkinson and colleagues[3] (from our group) to make the same point. In fact, this study was of 398 general ICU patients (not 101 patients as they suggest), and is the largest immunonutrition study so far published. The results referred to by Kennedy and Hall actually relate to the 'early successful feeder' (2.5 litres of feed administered in the first 72 h of ICU stay) subgroup of 101 patients. Whilst it is true that the reduction in hospital length of stay (15.5 *vs* 20 days, $P=0.03$) in this group was no longer significant at the $P<0.05$ level after censoring for mortality, feed formulation *and* hospital outcome, both remained significant independent determinants of hospital length of stay in the logistic regression analysis. This suggests that the benefit from immunonutrition could not be explained by differences in early death rate.

In a larger meta-analysis of 1482 patients from 12 studies published recently,[4] also from our group, this matter was addressed specifically by performing intent-to-treat analyses before and after censoring for mortality. There was no overall effect of immunonutrition upon mortality (relative risk 1.05, CI 0.78–1.41, $P=0.76$), and the significant reductions in hospital length of stay, relative risk of infection and number of ventilator days were all present before and after censoring for mortality.

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A number of other studies in this field also deserve consideration. In 1998, Houdijk and colleagues reported a reduction in infectious morbidity in 72 multi-trauma patients using an immunonutrition formulation enriched with glutamine.[5] In 1999, Gadek and colleagues administered an immune-enhancing enteral formulation to 146 patients with acute respiratory distress syndrome and also showed noteworthy benefits.[6] There were significant reductions in ventilator days, intensive care days and in the incidence of new organ failures. This year, Galban and colleagues published a study of 181 medical ICU patients with sepsis comparing IMPACT with a control feed, and demonstrated a significant reduction in mortality (19.1% *vs* 28.9%, *P*=0.05) in the IMPACT group.[7] We can only assume that the editorial was submitted before the publication of any of these studies, but most had been presented at critical care meetings and in abstract form over the past few years.

It is true that the value of immunonutrition in critically ill patients is not absolutely proven, and more research is certainly needed. However, there is now a substantial body of consistent evidence, incorporating more than 2500 patients, that strongly suggests that immunonutrition is not harmful and very likely to be beneficial. It is disappointing that an editorial on such an important and topical subject, and in a reputable journal, should be so dismissive of the potential value of this exciting approach, whilst at the same time ignoring so much of the recent literature.

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Conflict of Interest

Drs Wyncoll and Beale have received research grants from Novatis Nutrition and have been involved with two randomized studies with Impact, which were supported by Novartis.

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7 Galban C, Montejo JC, Mesejo A, *et al.* An immune enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care patients. *Crit Care Med* 2000; **28**: 643–8

Editor—Griffiths's defence of total parenteral nutrition (TPN) and Wyncoll and Beale's enthusiasm for immunonutrition are to be expected in view of their well-known interests in these areas. The editorial was submitted in December 1999 and so could not include articles published in 2000, nor was it appropriate to cite all the literature in a communication of this type. However, following perusal of the most recent literature we stand by the main conclusions of the editorial.[1]

Griffiths's curt dismissal of the meta-analysis of TPN is ill judged and he fails to recognize the importance of this major work from a group of international repute published in a journal of great influence—*JAMA*.[2] Furthermore, he fails to produce any substantial evidence to support his case: two citations drawing attention to problems with enteral nutrition[3 4] and a surgical paper simply describing the use of TPN in patients with severe acute pancreatitis.[5] We note that the use of TPN alone in pancreatitis was associated with a significantly greater mortality than enteral nutrition (60% *vs* 24%); more severe disease or a contribution from TPN? Otherwise, we agree with many of the questions raised by Griffiths about how future research in this difficult area should be conducted, in particular the implications of using pharmaceutical companies to fund such trials.

Wyncoll and Beale's view that we misquoted the work of Atkinson, Sieffert and Bihari[6] is correct in that we chose to select data from the study that showed a beneficial effect of immunonutrition (early successful feeder group, 2.5 litres of feed administered in first 72 h of ICU stay, *n*=101). We did not discuss the results of the 398 patients enrolled in the study because they failed to show any beneficial effects of immunonutrition on duration of ventilation, length of ICU stay and length of hospital stay! We are perplexed, therefore, at their 'extreme disappointment'. We attach little importance to multiple regression analysis that uses an outcome measure, length of hospital stay, when it is influenced by so many other factors unrelated to the severity of critical illness. The other studies cited by Wyncoll and Beale that 'we ignored' relate to the use of glutamine supplementation only[7] (another false dawn in metabolic support of the critically ill?), the introduction of immunomodulators, gamma-linolenic acid and antioxidants,[8] and a six-centre study of the effects of Impact on mortality and bacteraemia in sepsis.[9] There are no new clinical insights in these investigations and we are concerned about the use of novel immunomodulators while there is inadequate scientific evidence to support the use of existing compounds.

The current zeal for immunonutrition, and the results of initial trials suggesting beneficial effects, are reminiscent of the early days of research in TPN. Our editorial contained a plea for appropriate studies to be undertaken in immunonutrition to avoid the debacle that has ensued with TPN. We were not dismissive of the technique, but cautioned against its acceptance on the available evidence. It is imperative that new treatments are based on rigorous, scientific research and subjected to correctly designed, prospective, randomized controlled trials. Otherwise, Griffiths's intriguing suggestion, that levels of treatment should be withdrawn from patients in ICU until it is shown that the outcome is significantly worse, may start to appeal to those who question the voracious appetite of some intensivists for novel unproven therapies.

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1 Kennedy BC, Hall GM. Metabolic support of critically ill patients: parenteral nutrition to immunonutrition. *Br J Anaesth* 2000; **85**: 185–8
2 Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998; **280**: 2013–9

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9 Galban C, Montejo JC, Mesejo A, *et al.* An immune enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care patients. *Crit Care Med* 2000; **28**: 643–8

Pre-operative evaluation of the cervical spine in rheumatoid arthritis using dynamic magnetic resonance imaging

Editor—We write to emphasize the value of magnetic resonance imaging (MRI) of the cervical spine prior to surgery in patients with rheumatoid arthritis. The cervical spine has been reported to be involved in 50–80% of patients with rheumatoid arthritis, with cervical spine instability present in 25–50% of those with longstanding disease.[1] Pre-operative cervical radiographs are recommended for all patients with rheumatoid arthritis to identify those with significant cervical instability (particularly atlantoaxial and subaxial subluxation) who are at risk of cord compression during laryngoscopy and tracheal intubation. In this sub-group, anaesthetic techniques that avoid unprotected manipulation of the neck should be utilized.[2]

A complete series of cervical spine radiographs (lateral views of the neck in flexion and extension, a frontal view of the entire cervical spine and a frontal 'open-mouth' view of the odontoid process of the second cervical vertebra) is required to diagnose cervical spine instability. Kwek and colleagues,[3] however, reported inadequate pre-operative cervical spine x-rays in 36% of patients with rheumatoid arthritis scheduled for elective orthopaedic surgery, adequate but incomplete in 59% of patients and complete in only 5%.

MRI is vastly superior to plain radiographs for imaging the cervical spine. It allows direct visualization of the cervical cord, the craniocervical junction, the medulla, adjacent cerebrospinal fluid spaces, craniocervical and transverse ligaments, and the extent of pannus formation.[4] In patients with rheumatoid arthritis, sagittal and axial MR images obtained in flexion and extension (functional MRI) are particularly useful for demonstrating atlantoaxial and subaxial subluxation and the presence of cord compression and myelopathy. Associated disc disease that may be present in the mid- and lower cervical spine will also be demonstrated using the same imaging sequences. Using the rapid imaging sequences that are available on most modern MR scanners, a complete MRI examination of the cervical spine can be completed in less than 10 min, which compares favourably with the time required to acquire the four standard plain radiographic views of the neck.

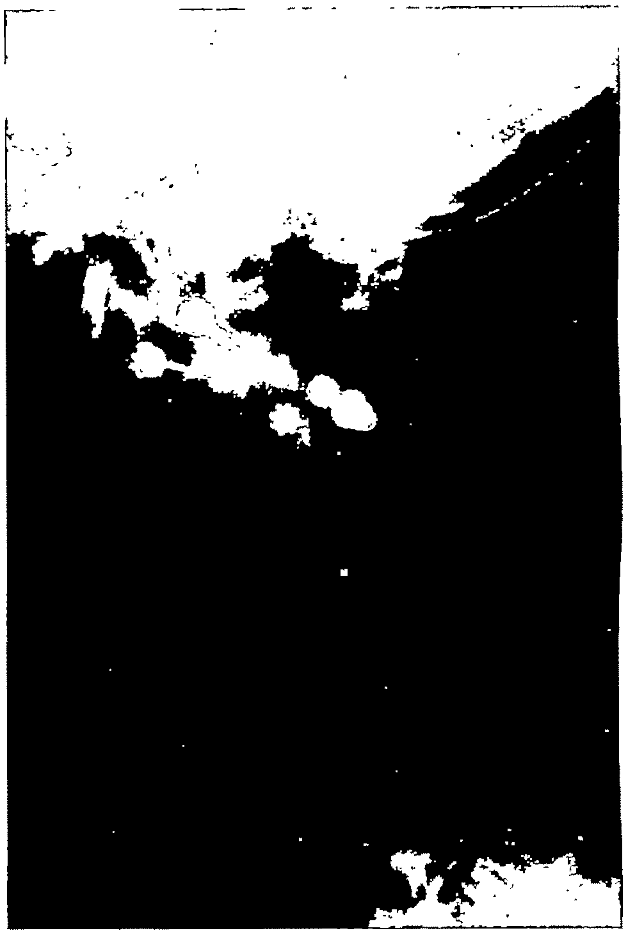

Fig 1 A lateral plain radiograph of the cervical spine acquired in flexion. The anterior arch of C1 and the odontoid process of C2 are obscured by the patient's earrings which could not be removed.

The benefits of performing pre-operative MRI of the cervical spine are highlighted by Figures 1 and 2. These images were obtained prior to elective knee replacement in a 68 year old female with a 20 yr history of rheumatoid arthritis. The patient complained of mild intermittent neck pain but had no clinical evidence of nerve root compression or myelopathy. Adequate plain radiographs of the cervical spine could not be obtained as the patient's earrings could not be removed (Figure 1). MRI of the cervical spine demonstrated severe atlantoaxial subluxation on neck flexion resulting in compression of the craniocervical junction (Figure 2). Knowing the severity of atlantoaxial subluxation, the patient's anaesthetic management was planned to protect the spine using awake fiber-optic intubation.

Although MRI is superior to plain radiographs for evaluating the cervical spine, economic and logistic reasons prevent its routine pre-operative use in all patients with rheumatoid arthritis. A recent and complete series of cervical spine plain radiographs is required prior to anaesthesia in all patients with rheumatoid arthritis. MRI should be reserved for patients in whom plain radiographs are inadequate as up to 50% of rheumatoid patients will have undiagnosed cervical spine instability.

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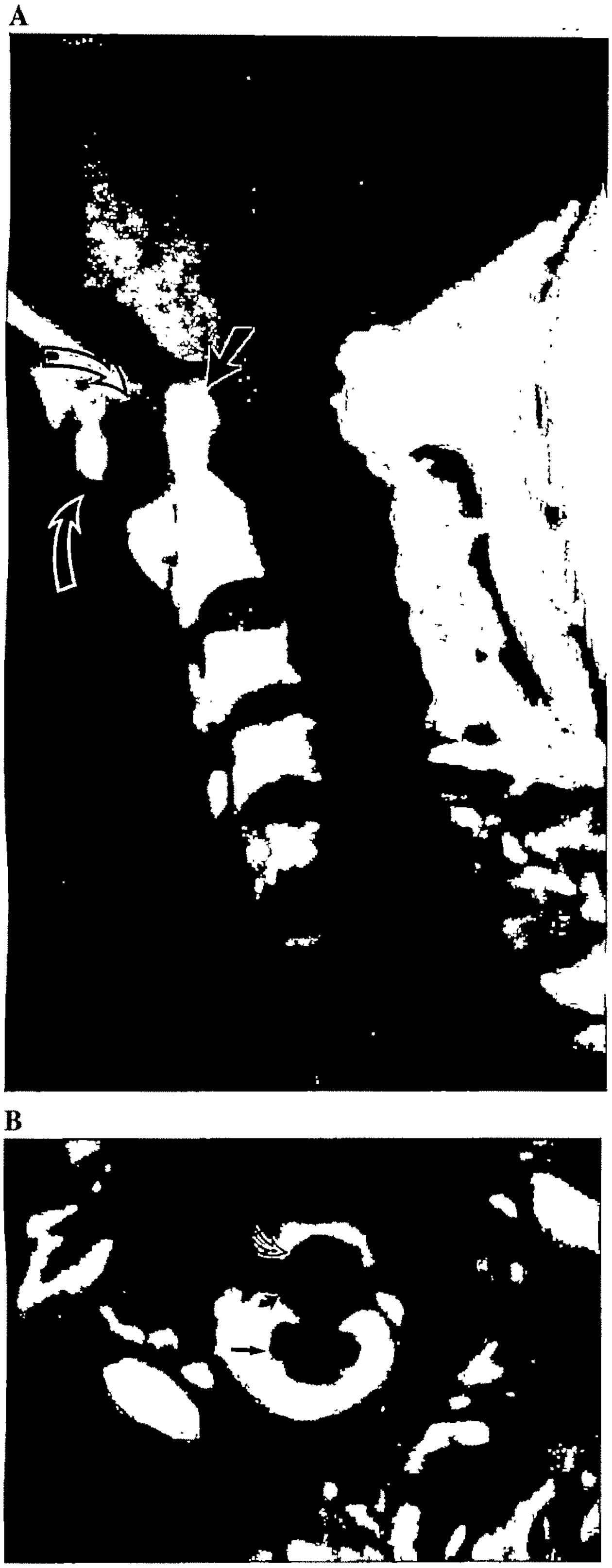

Fig 2 (A) A sagittal T1-weighted MR image in flexion demonstrates gross atlantoaxial subluxation with the odontoid process of C2 (straight black arrow) displaced 10 mm posterior to the arch of C1 (curved white arrow) and extensive intervening pannus (curved black arrow). The upper cervical cord is compressed by the posteriorly displaced odontoid process. (B) An axial T2-weighted image in flexion demonstrates anterior compression of the cervical cord (straight arrow) by the odontoid process of C2 (open arrow) and gross laxity of the transverse ligament (short curved arrow).

1 Conlon PW, Isdale IC, Rose BS. Rheumatoid arthritis of the cervical spine. An analysis of 333 cases. *Ann Rheum Dis* 1966; **25**: 120–6
2 Skues MA, Welchew EA. Anaesthesia and rheumatoid arthritis. *Anaesthesia* 1993; **48**: 989–97
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Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults

Editor—The paper of Kong and colleagues[1] is interesting from an academic point of view, in showing that the high incidence of complications associated with induction of anaesthesia with desflurane may be modified by pretreatment with opioid analgesics. I would question the *practical* significance of this finding. As a regular practitioner of inhalation induction (using sevoflurane), I have observed the following advantages to the technique: (i) a rapid, smooth induction of anaesthesia which is clinically indistinguishable from propofol;[2 3] (ii) minimal apnoea, retaining respiratory rate and pattern as a useful guide to anaesthetic depth; (iii) popular with needle phobics; (iv) cardiovascular stability and (v) rapid emergence after brief procedures compared to propofol induction.[2] Kong and colleagues have demonstrated cardiovascular stability with their technique, but this is hardly surprising given the slow induction time. Most anaesthetists would probably regard a time to loss of responsiveness of 4 min as excessive for routine use. The requirement for opioid pretreatment effectively increases this time to 9 min. It would presumably take even longer before a laryngeal mask or tracheal tube could be inserted. In addition, the use of intravenously administered opioids removes the advantage for needle phobics and is likely to delay awakening. Apnoea still occurred with opioid use and the duration of this effect was not stated.

Kong and colleagues claim that the incidence of coughing and excitement with opioid-modified desflurane is comparable to that obtained with sevoflurane. I feel that they have been very selective in the references which they have quoted.[4–6] All of the studies cited involved very small numbers of subjects (10–20 per group), so the percentage values for adverse effects are unreliable. In addition, they all used an incremental tidal breathing induction technique, in which the concentration of sevoflurane was gradually built up from a low level. This is probably the least advantageous way in which to administer sevoflurane. With a vital capacity induction (using 8%), coughing typically occurs in 3–4% of patients.[7 8] Using a tidal breathing technique in which 8% sevoflurane is administered from the outset also reduces coughing to 2% or less.[2 3 9] Avoiding the incremental induction technique similarly reduces the incidence of excitement to very low levels. Finally, this study on desflurane specifically excluded patients who smoked, a group highly likely to experience respiratory complications on induction. In contrast, the published studies with sevoflurane (in adults) all included smokers.

Although it is interesting to see that the induction characteristics of desflurane can be tamed somewhat, it would still seem sensible to choose the agent with the most favourable set of properties when performing an inhaled induction.

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Conflict of Interest

I have previously received research funding and lecture fees from Pharmacia-Upjohn, the former distributor of desflurane. However, I have received considerably more research funding and lecture fees from Abbott, the manufacturer of sevoflurane.

1 Kong CF, Chew STH, Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85**: 264–7

2 Thwaites A, Edmends S, Smith I. Inhalation induction with sevoflurane: A double-blind comparison with propofol. *Br J Anaesth* 1997; **78**: 356–61

3 Smith I, Thwaites AJ. Target-controlled propofol *vs* sevoflurane: A double-blind, randomised comparison in day-case anaesthesia. *Anaesthesia* 1999; **54**: 745–52

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7 Philip BK, Lombard LL, Roaf ER, Drager LR, Calalang I, Philip JH. Comparison of vital capacity induction with sevoflurane to intravenous induction with propofol for adult ambulatory anesthesia *Anesth Analg* 1999; **89**: 623–7

8 Smith I, Terhoeve PA, Hennart D, Feiss P, Harmer M, Pourriatt JL, Johnson IAT. A multicentre comparison of the costs of anaesthesia with sevoflurane or propofol. *Br J Anaesth* 1999; **83**: 564–70

9 Sigston PE, Jenkins AMC, Jackson EA, Sury MR, Mackersie AM, Hatch DJ. Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. *Br J Anaesth* 1997; **78**: 362–5

Editor—Thank you for the opportunity to reply to Dr Smith's comments from Keele University, regarding our use of intravenous narcotics, to reduce the incidence of airway irritability during desflurane induction in adults.[1]

Smith quotes five studies[2–6] in support of his argument that we have been selective in our choice of previous work to compare our findings with those obtained with sevoflurane induction. In Table 1, we have combined our own results with those computed from these very same studies.

Based on these figures, we see no reason to dispute our comment that i.v. narcotics reduce the incidence of airway irritation from desflurane induction to that comparable to sevoflurane. Clearly, as we have mentioned in our paper,[1] it would be desirable to directly compare the two agents in a randomized controlled study in a given population sample.

As practising anaesthetists, we agree with the advantages quoted by Smith in the use of sevoflurane for inhalational induction, and have reported on our favourable experience in its use in difficult airway management.[7] Hence, we do not suggest that desflurane induction is a substitute for sevoflurane in all situations. However, the use of desflurane is safer when rapid emergence and shorter time to extubation[8] are essential. To dismiss our results as being merely of 'academic' rather than of 'practical' interest is contrary to the practice of evidence-based medicine.

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Conflict of Interest

None.

1 Kong CF, Chew STH, Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85**: 364–7

2 Thwaites A, Edmends S, Smith I. Inhalation induction with sevoflurane: A double-blind comparison with propofol. *Br J Anaesth* 1997; **78**: 356–61

3 Smith I, Thwaites AJ. Target-controlled propofol *vs.* sevoflurane: a double-blind, randomised comparison in day-case anaesthesia. *Anaesthesia* 1999; **54**: 745–52

4 Smith I, Terhoeve PA, Hennart D, Feiss P, Harmer M, Pourriatt JL, Johnson IAT. A multicentre comparison of the costs of anaesthesia with sevoflurane or propofol. *Br J Anaesth* 1999; **83**: 564–70

5 Sigston PE, Jenkins AMC, Jackson EA, Sury MR, Mackersie AM, Hatch DJ. Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. *Br J Anaesth* 1997; **78**: 362–5

6 Philip BK, Lombard LL, Roaf ER, Drager LR, Calalang I, Philip JH. Comparison of vital capacity induction with sevoflurane to intravenous induction with propofol for adult ambulatory anesthesia *Anesth Analg* 1999; **89**: 623–7

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Epidural analgesia during labour

Editor—In an attempt to answer the hotly debated question of whether epidural analgesia in labour affects Caesarean section rate, Loughnan and colleagues[1] conducted a randomized controlled trial on 802 nulliparous women. Six hundred and fourteen women requested additional analgesia in childbirth and this group was analysed. This study is an extremely difficult one to perform, and should be applauded. Women were allocated earlier in pregnancy via sealed envelopes to receive either pethidine or epidural analgesia. When the subgroup who requested analgesia

Table 1 Comparison of desflurane induction[1] (C=control, M=morphine, F=fentanyl) with suggested papers[2–6] using sevoflurane (S)

Study	Kong[1]	Kong[1]	Kong[1]	Thwaites[2]	Smith[3]	Smith[4]	Sigston[5]	Philip[6]
n	60	60	60	51	30	69	25	32
Group	C	M	F	S	S	S	S	S
Cough	25%	8.3%	5.00%	1.9–8%	–	4.3%	–	3%
Apnoea	20%	5.0%	13.30%	16%	60%	–	4%	–
Excitatory movements	46.7%	8.3%	16.7%	9.8%	10%	2.9%	16%	0%
Laryngospasm	11.7%	1.7%	3.30%	–	–	2.9%	8%	6.25%

was analysed on an 'intention-to-treat' basis, the study concluded that the incidence of Caesarean section was not increased with the use of epidural analgesia. The intention-to-treat analysis shows without bias the effect of offering the treatment, whether or not it is accepted.

Women at the time of recruitment (28–30 weeks gestation) are being asked to consider their wishes about analgesia in a labour which is 9–14 weeks hence. Their level of anxiety, pain and excitement, in a process which none have previously experienced, will vary greatly from the time of consent. Many weeks of influence from magazines, literature, peers and clinicians encountered antenatally will influence their wishes to abide by the decision within the envelope. Many who previously thought that they might be amenable to one particular analgesic option were clearly not when the time came: 175 women randomized to receive pethidine (56.5%) actually chose an epidural, compared to 257 randomized to the epidural group (84.5%), a difference in epidural usage of only 28.1%. This will greatly dilute any estimate of the treatment effect. The effect of the anaesthetist siting an epidural (as opposed to offering one) may be 3.56 (i.e. 100/28.1) times the value reported.

Although the design used may be the best available given the constraints of consent in labour, and the difficulty of withholding effective analgesia, it does affect the findings. To analyse these women meaningfully within their original group (as in an intention to treat analysis) assumes that their deviation from the assigned method of analgesia is independent of outcome, i.e. the Caesarean section rate. As the reasons for cross-over are highly associated with need for intervention (e.g. prolonged labour), this is clearly not the case. In this case, a high proportion of women who receive an epidural are analysed as if they have not.

To prove no effect is impossible. For two treatments to be equivalent, the difference between them must be too small to be clinically important. This is tested by looking at the confidence interval, and in particular at the upper bound. We believe that clinicians would agree that an absolute increase of 4% or more in the Caesarean section rate would definitely be clinically important (e.g. from 13% to 17%). Smaller increases (e.g. 2% or 3%) would also be relevant.

The actual difference in Caesarean section rate between the two arms was –1.1%, with 95% confidence limits of –6.3 to 4.1. After allowing for cross-over, this may reflect a true difference of –3.8%, 95% CI –22.3% to 14.8%. Whether this correction is used or not, the upper bounds are much too large to be dismissed. One cannot conclude from this study that epidurals do not influence the Caesarean section rate; the jury must still be out.

Exactly the same limitations apply to the meta-analysis[2] quoted in the accompanying editorial.[3] The confidence interval for the odds ratio from 0.81 to 2.76 includes clearly important values relating epidural use to Caesarean section rate, even before allowing for any dilution of effect due to cross-overs.

We fear that the advantages of intention-to-treat analysis and a randomized design will always be limited in studies of epidural use in labour. Investigators must continue to consider the impact of regional analgesia on obstetric outcome including the Caesarean section rate. The importance of this study should not be ignored, but it does not provide a definitive answer.

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1 Loughnan BA, Carli F, Romney M, Dore CJ, Gordon H. Randomized controlled comparison of epidural bupivacaine versus pethidine for analgesia in labour. *Br J Anaesth* 2000; **84**: 715–9
2 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs. Parenteral opioid analgesia on the process of labor. *JAMA* 1998; **280**: 2105–10
3 Russell R. The effects of regional analgesia on the progress of labour and delivery. *Br J Anaesth* 2000; **84**: 709–12

Editor—Kenyon, Seed and Shennan advise caution when interpreting the results of the randomized study by Loughnan and colleagues,[1] in which the use of epidural analgesia was not associated with an increased incidence of Caesarean section. Furthermore, they question the validity of a meta-analysis of other such randomized studies[2] cited in the accompanying editorial.[3] Their concern is that no conclusion can be drawn on the relationship between analgesia and labour outcome based on the statistical methods that have been used. I would wholeheartedly agree with this worry. However, my views are based not on the grounds of statistics but on the more fundamental issue that in such randomized studies investigators are not blinded to the treatment group. As was stated in the editorial, such methodology introduces a potential source of observer bias that is of far greater importance than how one chooses to view confidence intervals. To avoid the issue of observer bias, impact studies, in which delivery outcome is assessed during changes in the use of regional analgesia, are more useful. Such studies have repeatedly failed to demonstrate a rise in obstetric intervention despite often dramatic increases in the number of women choosing an epidural for labour analgesia. Although relying on comparison with historic controls, such studies may provide the answer to the relationship between epidurals and delivery outcome. By modifying the management of labour in those women receiving regional analgesia, increases in instrumental and operative deliveries may be prevented.

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1 Loughnan BA, Carli F, Romney M, Dore CJ, Gordon H. A randomized controlled comparison of epidural bupivacaine versus pethidine for analgesia in labour. *Br J Anaesth* 2000; **84**: 715–9
2 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs. Parenteral opioid analgesia on the process of labor. *JAMA* 1998; **280**: 2105–10
3 Russell R. The effects of regional analgesia on the progress of labour and delivery. *Br J Anaesth* 2000; **84**: 709–12

Editor—Thank you for the opportunity to reply to the letter by Kenyon and colleagues. During the initial phase of our trial, women were approached at 36 weeks gestation, but we found that by this stage of pregnancy the majority had already chosen their preferred type of analgesia. We therefore approached women earlier in pregnancy, at 28–30 weeks gestation, to discuss whether they would consider joining the trial. When additional analgesia was requested during labour, the midwife confirmed that the woman was still willing to participate, before opening the envelope containing the randomized treatment assignment. Every effort was made to minimize the number of women who crossed over between the two randomized treatments. However, for ethical reasons we considered it essential that all women randomized to pethidine were able to subsequently request epidural analgesia for uncontrolled pain.

Table 1 Number of, and reasons for, intervention

Reason for operative/instrumental delivery	Epidural number (%)	Pethidine number (%)
Failure to progress	19 (53)	21 (57)
Fetal distress	16 (44)	14 (38)
Other	1 (3)	2 (5)
Total	36	37

We do not consider the proposed method of adjustment for cross-over to be appropriate. Women who cross over are not a random subset of those allocated to a particular treatment. Table 2 in our paper clearly demonstrates that women who received both pethidine and epidural had on average longer labours, requested additional analgesia earlier in labour and were more likely to have been induced.

We tried to obtain an estimate of the effect of epidural analgesia using a logistic regression model, but none of the obstetric characteristics recorded before randomization could explain the difference in Caesarean section rates between those who accepted and those who refused their randomized treatment. We consider that the intention to treat analysis provides the least biased estimate of the effect of epidural analgesia on the Caesarean section rate.

The reasons for instrumental/operative delivery are summarized in Table 1. Both the total number of, and reasons for, the intervention are reassuringly similar in the two randomized groups.

We reported the results of a pragmatic trial comparing a treatment policy of offering epidural or pethidine to women in labour requesting additional analgesia. While our study alone cannot prove that epidurals do not increase the Caesarean section rate, it is in agreement with the conclusions of Halpern and colleagues in their systematic review of all randomized comparisons of epidural and pethidine analgesia during labour and contributes to the body of evidence available.[1]

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1 Russell R. The effects of regional analgesia on the progress of labour and delivery. *Br J Anaesth* 2000; **84**: 709–12

Low-dose spinal morphine for postoperative analgesia following knee arthroplasty

Editor—We read with interest the article by Cole and colleagues.[1] Provision of good analgesia for patients after knee arthroplasty remains a challenge and the authors are to be congratulated on their clear confirmation of the efficacy of intrathecal morphine, both in terms of reduction of VAS scores and overall opiate consumption in this context. We do wish, however, to make the following points regarding other important aspects of the study.

Perhaps the most novel contribution of this study is its detailed investigation of the respiratory side-effect profile of intrathecal morphine. While inferences may be drawn from the absence of statistically significant differences between the groups for the respiratory indices measured, unfortunately, this study is not adequately powered to support the drawing of such conclusions. In the light of this, it is clear from the data presented that there are grounds for reservations regarding the use of this dose of intrathecal morphine in this patient group. A substantially greater number of significant arterial haemoglobin desaturations (35% *vs* 20%) are reported in the group receiving intrathecal morphine. Of further concern, these patients spent a far greater proportion (median 10% *vs* 3%) of their first 13–14 postoperative hours with a haemoglobin oxygen saturation below 95%. In addition, the authors state that 'twice as many [patients in the morphine group] were classified as 'hypoxaemic patients'; that is they spent greater than 20% of their time with mild or moderate hypoxaemia'. We are unsure of the utility or validity of the reported oxygen saturation results for each group, which appear to represent the median of the mean oxygen saturation values from each patient. The authors go on to state that a substantially larger study would be required to confirm or exclude the presence of an increased risk of respiratory depression, but have not included a sample size calculation, based on the data presented, to support this contention. We would contend that the incidence of respiratory side-effects seen in this small study warrants fuller investigation, before this dose of intrathecal morphine could be recommended in this patient group.

This study also reports higher levels of less severe, but nevertheless distressing side-effects, including emesis requiring treatment (60% *vs* 38%), and pruritus (27% *vs* 14%) in patients receiving intrathecal morphine. The incidence of nausea or urinary retention is not presented, but would also be of interest. The relatively high reported incidence of both minor and more severe side-effects raises questions regarding the appropriateness of the dose of morphine used. It is interesting that the authors referred to a relatively old dose-finding study in patients after hysterectomy,[2] as a guide to the most appropriate intrathecal morphine dose. As the authors state, there are more recent studies attesting to the efficacy of smaller doses in patients undergoing lower limb joint arthroplasty.[3 4] While there is a paucity of data specifically referring to knee arthroplasty, there is at least one older report attesting to the efficacy of lower doses of intrathecal morphine in arthroplasty patients, which might have provided a more appropriate guide.[5]

The authors state in the methods section that patients in the study were given a general anaesthetic with propofol and fentanyl 'at the discretion of the anaesthetist'. Why were patients given a general anaesthetic, in addition to a spinal anaesthetic? Was failure of the spinal anaesthetic to provide adequate anaesthesia an indication? There is no documentation of how many patients received a general anaesthetic, which groups these patients were in, or explanation of why a general anaesthetic technique was used in addition to a neuraxial block. Furthermore, there is no evidence presented that the spinal anaesthetic was effective in all the patients studied, a requirement in patients also receiving a general anaesthetic. Clearly, these issues are of importance, particularly in a study of postoperative respiratory side-effects.

The authors provide a satisfactory explanation for the exclusion of one patient from each group from the analysis, and further explain the loss of postoperative respiratory data. While the problems of collecting a comprehensive data set in postoperative patients are appreciated, they fail to explain the substantial loss of patient data on emesis (5 patients), pruritus (7 patients), satisfaction (4 patients), and pain severity (5 patients). In the latter example, VAS pain scores are reported for 34 patients, 17 (out of 18) in each group, but pain severity is only reported for 14 of the 18 patients who received intrathecal morphine. Furthermore, different numbers of patients are missing for each data set, which adds to the difficulties in interpretation. Data loss of this magnitude, in a study of this size may constitute a source of accidental bias.

Lastly, on a smaller point, the authors refer to a recent study demonstrating efficacy of intrathecal morphine 0.1 mg for analgesia after hip replacement. However, the reference quoted, Gerancher and colleagues,[6] refers to the efficacy of intrathecal morphine in patients after Caesarean section. Presumably the authors intended to reference Slappendal and colleagues,[3] which they have included in their bibliography. Alternatively, another recent demonstration of the efficacy of intrathecal morphine 0.1 mg has been reported by Mendieta-Sanchez and colleagues.[4]

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Editor—Thank you for the opportunity to respond to the letter from Laffey and Flynn who raise important issues concerning the optimal dose of intrathecal morphine and the significance, or lack of it, of the respiratory effects demonstrated in our study.

We would agree that there is now increasing evidence to support the efficacy of doses of intrathecal morphine as low as 0.1 mg. However, these studies have investigated patients recovering from Caesarean section[1–3] or hip replacement[4] and not knee replacement. Two of the studies quoted by Laffey and Flynn were not published until 1999 by which time our study was completed. The protocol for our study was written in 1996 when the available dose response studies[5 6] suggested that intrathecal morphine 0.3 mg was an effective dose with minimal side-effects. This dose of opioid has been frequently used in our clinical practice and appeared to provide good quality postoperative analgesia. We therefore elected to use intrathecal morphine 0.3 mg for this study.

The power calculation was based on the primary aim of the study, which was to investigate the efficacy of intrathecal morphine following knee arthroplasty since little had been written on this subject. However, due to concerns about early and delayed respiratory depression we elected to study the respiratory effects in this group of patients, but this was a secondary aim. There is a paucity of literature in this area as continuous respiratory monitoring is labour intensive and the results are often difficult to analyse and present in a meaningful way.

We presented data on the incidence of hypoxaemia (using previously published criteria), the median oxygen saturation and the respiratory distress indices (RDI) in the two groups. Although there were no significant differences between the groups apart from a small difference in median oxygen saturation, we share Laffey and Flynn's concern that intrathecal morphine 0.3 mg was associated with clinically significant hypoxaemia in one of the study patients. This concern and the need for further studies to elucidate the optimal opioid and dose for intrathecal use were emphasized in the discussion.

Following our study we have changed to a more lipophilic intrathecal opioid and currently use diamorphine 0.3 mg routinely with less theoretical risk of rostral spread and delayed respiratory depression. It would be interesting to compare the efficacy and respiratory effects of this dose of diamorphine with the lower dose of morphine advocated above.

To clarify some practical aspects of the study, the anaesthetic management of the patients was standardized, and all of the patients received a combined spinal and general anaesthetic, as this was the current practice in the department during the study period.

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1 Swart M, Sewell J, Thomas D. Intrathecal morphine for Caesarean section: an assessment of pain relief, satisfaction and side effects. *Anaesthesia* 1997; **52**: 364–81
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4 Slappendal R, Weber EW, Dirksen R, Gielen MJ, Van Limbeek J. Optimisation of the dose of intrathecal morphine in total hip surgery: a dose finding study. *Anesth Analg* 1999; **88**: 822–6
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6 Jacobson L, Chabal C, Brody MC. A dose-response study of intrathecal morphine: efficacy, duration, optimum dose, and side effects. *Anesth Analg* 1988; **67**: 1082–8

Oral ketoprofen in children—could it have been done differently?

Editor—Tuomilehto and colleagues[1] set out to compare the efficacy of oral and intravenous ketoprofen in children undergoing adenoidectomy. They also compared the two treatments with children having neither form of ketoprofen. We have a number of questions.

It is interesting that the study shows that ketoprofen produces better analgesia when given intravenously than when given orally. The results are based on observed behaviour—the need for rescue analgesia and the Maunuksela pain scale—yet these results are at odds with each other. In addition, the conclusions drawn in the text differ from the results in the table. Neither of the study groups had pain scores outside the 'moderate' band at rest, but the placebo group only had 'slight' pain at rest. All groups were within the 'moderate' band during swallowing. It is disappointing that the median scores were not in the 'mild' band for the ketoprofen groups, suggesting that the clinical effect is not dramatic. Fewer children in the oral group required rescue analgesia, but those who did needed more doses than in the intravenous group. The study only compares number of doses of fentanyl given to those who received it rather than the total number of doses received by each group as a whole. Surely it would have been more logical to compare the total number of doses given to each group: would there then still be a significant difference?

Can children between the ages of one and nine years really be assessed using a single pain scale and the results compared? It is suggested[2] that only children over the age of four years old should be included when using the Maunuksela scale to assess analgesic efficacy, which was not the case in this study. From the paper it is unclear as to what the Maunuksela pain scale is. Indeed, even in the original description of the scale[2] we could not find a clear definition of it. Pain scores[3] are classified as 0 (no pain), 1–3 (slight pain), 4–6 (moderate pain), 7–9 (severe pain) and 10 (worst possible pain). Most pain scores were within the 'moderate' band making statistical analysis unlikely to yield significant results. Also if a placebo group is to be included in the study then the three groups should be of equal size. However, if the aim is to compare intravenous with oral ketoprofen then why include the placebo group? Is it really ethical to give less analgesia to a group of children in the knowledge that their pain is likely to be worse? The study appears to be too small to produce meaningful results. We are not sure that the conclusions drawn are valid in the light of the results obtained. Did the authors really achieve their aim?

Randomized controlled trials are always cited as the gold standard for determining analgesic efficacy. However, they often need large numbers of subjects and can be flawed in design. A recent editorial in the *British Medical Journal*[4] suggested that a good observational study may be more valuable than a flawed randomized controlled trial. Surely a good quality audit looking at large numbers, using oral ketoprofen, and following on from the authors' previous work, would have produced more meaningful results.

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1 Tuomilehto H, Kokki H, Tuovinen K. Comparison of intravenous and oral ketoprofen for postoperative pain after adenoidectomy in children. *Br J Anaesth* 2000; **85**: 224–7
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4 Barton S. Which clinical studies provide the best evidence? *Br Med J* 2000; **321**: 255–6

Editor—We are pleased to note that our article has interested your readers and we are more than willing to reply to the important questions raised by Garstang and Price.

We agree absolutely that children's behavioural response to pain varies greatly with age, young children under four years being probably the most difficult to interpret. However, in this age group a great number of minor day-case procedures are done; for example, in France in 1996, over 200 000 anaesthetic procedures were performed in this age group. Of these, two-thirds were ear-, nose- and throat procedures.[1] This is the reason we believe that research in evaluating postoperative pain treatment in young children is clinically essential, despite the difficulties confronted when working with them. As we wrote in our discussion, pain assessment in small children is difficult because of their limited verbal abilities and understanding.[2] Consequently, for young children, pain scales with assessment based on multiple variables are recommended. The Maunuksela pain scale used in our study is a multidimensional assessment based on physiological, behavioural and contextual indicators, and it has been validated for use in children from 1 to 18 years.[3]

The original report and our own experience show that the Maunuksela pain scale correlates well with other observational pain scales and also with pain reported by patients themselves.[3 4] Moreover, a good internal consistency has been observed.[3] Accordingly, the Maunuksela pain scale can be used in clinical analgesic studies in children older than one year.

A placebo group was included as a negative control to avoid study bias. It was considered ethical because all the children received an opioid at induction and were allowed more opioid whenever needed (pain score 3 or higher on a scale 0 to 10) as a rescue analgesic. In the present study, 40 children in the i.v. group received 45 doses of fentanyl in the recovery room, whereas 40 children in the per oral group received 58 doses and 20 children in the placebo group received 33 doses.[2]

Although we agree with Garstang and Price that a larger number of subjects could have been used, we believe that to provide a meaningful answer to a clinical rather than statistical issue, the number of patients was sufficient.

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1 Clerque F, Auroy Y, Péquignot F, *et al.* French survey of anaesthesia in 1996. *Anesthesiology* 1999; **91**: 1509–20
2 Tuomilehto H, Kokki H, Tuovinen K. Comparison of intravenous and oral ketoprofen for postoperative pain after adenoidectomy in children. *Br J Anaesth* 2000; **85**: 224–7
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Huntington's chorea

Editor—We were interested to read the case report from Nagele and Hammerie regarding Huntington's chorea.[1] We have also recently reported a similar case with a successful outcome[2] and would like to make the following comments.

Onset of Huntington's chorea in childhood may be a different disease from the adult form as there are several clinical differences between the two. Of particular relevance to anaesthetists is the increased risk of convulsions (50% compared to 2% in the adult form[3]) and the higher prevalence of rigidity as opposed to choreactic movement in children.[4] The precipitation of rigid spasms by postoperative shivering is therefore of particular importance in this group of patients. The absence of choreactic movement has led to the condition also being known as Huntington's Disease. The possibility of autonomic dysfunction should be remembered.[2 5]

It is useful that Nagele and Hammerie have added mivacurium and sevoflurane to the long list of drugs that have been used successfully in Huntington's chorea. These include fentanyl, alfentanil, midazolam, pancuronium, atracurium, Althesin and propofol.[6–10] As they mentioned, a delay in recovery reported 35 years ago after the use of succinylcholine[11] may have been due to the presence of an acquired reduction in plasma cholinesterase due to the patient's debilitated condition.[9] There are now at least three reports of the successful use of succinylcholine[1 3 9] in Huntington's chorea compared to one unsuccessful one.[11] As such, there seems little to support the risk of prolonged paralysis in these patients. In two case reports of an exaggerated response to thiopental in Huntington's chorea,[12 13] the patients were given what we would now regard as an overdose and delayed recovery is not surprising. It has been concluded that thiopental is not contraindicated but that it should be used with 'the same degree of caution as for any patient with debilitating disease'.[14] The use of thiopental in a patient at risk of convulsions may be beneficial. The evidence for sensitivity to midazolam is a single case report of a 64 kg man who received two doses of oral diazepam 5 mg in the 12 h prior to surgery. Fentanyl 50 µg and midazolam 5 mg were required to 'induced anaesthesia'.

There seems little justification for continuing the myth that patients with Huntington's chorea are at higher risk of intraoperative complications including a prolonged response to succinylcholine and thiopental and an increased sensitivity to midazolam. We suspect that delayed recovery and apparent increased drug sensitivity is more a feature of the debilitated clinical condition of the patient rather than a specific feature of the disease itself. Drugs that have been reported as safe to use in patients with Huntington's chorea will not be if they are used inappropriately.

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1 Nagele, P, Hammerle AF. Sevoflurane and mivacurium in a patient with Huntington's chorea. *Br J Anaesth* 2000; **85**: 320–1
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13 Blanloeil Y, Bigot A, Dixneuf B. Anaesthesia in Huntington's chorea. *Anaesthesia* 1982; **37**: 695
14 Browne MG. Anaesthesia in Huntington's Chorea. *Anaesthesia* 1982; **38**: 65

Editor—We appreciate the comments of Leng and Gupta on our case report that described the anaesthetic management of a patient with Huntington's chorea.[1] We agree that there is increasing evidence that patients with Huntington's chorea or Huntington's disease might respond normally to anaesthetic drugs.[2–4] Nevertheless, experience with these patients undergoing general anaesthesia is limited, since only a few cases have been reported in the literature over the past 35 yr. These reports show that patients with Huntington's chorea have a higher risk of postoperative complications including shivering and pulmonary aspiration whereas the intraoperative course is often uneventful. Appropriate use of anaesthetic drugs seems to be of secondary importance to preventing postoperative complications.

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1 Nagele, P, Hammerle AF. Sevoflurane and mivacurium in a patient with Huntington's chorea. *Br J Anaesth* 2000; **85**: 320–1
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Accidental detection of tracheal bronchus: alternative airway management

Editor—The article by Conacher made for interesting reading.[1] I agree with the author that although a tracheal bronchus can be detected preoperatively on a chest x-ray, accidental intraoperative finding is more likely. In such an event, working in a unit where equipment such as a fibreoptic bronchoscope is not available, managing the airway even for a non-thoracic procedure can prove to be a formidable challenge. The least one can do is to promptly detect the condition and properly reposition the tube as suggested by the author. But this repositioning may predispose to accidental extubation especially if the bronchial offset is proximal and the patient has to be positioned in the prone or lateral position for the surgical procedure.

I present an alternative approach to such management. In the event of suspicion of a tracheal bronchus, while withdrawing the tracheal tube to confirm the condition, the length of the part of the tube withdrawn is noted. Another uncuffed tracheal tube of the same size is taken. A hole (approximately 0.5 cm diameter) is made in the wall of this tube at a point from the tip of the tube corresponding to the length withdrawn of the first tracheal tube. The hole can be made on the side on which the tracheal bronchus is suspected. The existing tracheal tube is replaced with the one with a side hole ensuring the reinserted one is of the same total length. The new tube can be positioned with the help of auscultation of the apical zone and by monitoring oxygen saturation with a pulse oximeter to assure that the cut hole is aligned with the tracheal bronchus. Pharyngeal packing with moist ribbon gauze is done to seal any possible peritubal leak. The patient can then be positioned for the surgical procedure.

Care should be taken to use sterile means to make the hole and also to ensure that no cut pieces of the tube material remain sticking to the tube. Proper positioning of the hole and careful attention to tracheal tube fixation is important. This method is simple and easy to perform but changing the tracheal tube can pose problems in the case of difficult intubation.

Another alternative is the LMA[†], which however may not be preferred for use in all patient positions.

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1 Conacher ID. Implications of a tracheal bronchus for adult anaesthetic practice. *Br J Anaesth* 2000; **85**: 317–21

*LMA® is the property of Intavent Limited.

Editor—Thank you for the opportunity to reply to the suggestion of Dr Dubey to manufacture a Murphy eye in an uncuffed tracheal tube. In theory, it is a sound suggestion to use the first tube as a template to judge the alignment with the origin of a high-offset tracheal bronchus; and the prescription carries with it some useful caveats to make it safe. I agree, of course, there is always a LMA* for the difficult exotic airway.[1]

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1 Conacher ID, McMahon CC, Meikle D. 'Chicane like' airway as a complication of lingual tonsils. *Lancet* 1996; **348**: 475

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Book Reviews

Law for Doctors: Principles and Practicalities. Margaret Branthwaite. Published by The Royal Society of Medicine Press Limited, London. Pp. 80; glossary of legal terms and phrases; table of cases; table of statutes and statutory instruments; index. Price £7.50. ISBN 1-85315-465-2.

Every experienced 'expert' witness can bore guests at countless dinner parties with tales of conferences with barristers in medicolegal cases at which clinicians accused of negligence have displayed either complete ignorance or enormous misunderstanding of the relevant law and legal processes. Frequently, their misconceptions lead them to incorrect assumptions about the outcome of the litigation; some believe that they are at risk of professional ruin simply because negligence has been alleged, others believe that a predisposition to injury will act as a defence, and a proportion are convinced that they will be able to persuade a jury of their innocence at a trial in a civil court, failing to appreciate that the outcome is determined by a judge alone. In my experience, there is also a significant proportion of 'expert' witnesses who have little knowledge of the relevant law.

The aim of this book is to correct the ignorance and misunderstanding of clinicians. In the Preface, Dr Branthwaite indicates her objectives. 'This book sets out to provide health care professionals, particularly doctors, with sufficient understanding of the law to alleviate as far as possible those elements of concern which are founded on uncertainty, to assist them to participate more fully in discussions and decisions on cases with which they were involved and, above all, to have some idea of what to expect, be they required to assist the court or face legal action themselves.'

In my view, the book achieves these goals admirably. In 12 chapters, Dr Branthwaite summarizes the principles of negligence, legal procedures in civil litigation in England, the ways in which civil litigation is funded, the manner in which financial compensation is calculated, consent, complaints and disciplinary procedures, the coroner's court, and the criminal law. Relevant cases are cited in the text, and listed not only at the end of each chapter, but also in a global list, with cross-references to the chapter(s) in which citation occurs. Some aspects of the potential impact of implementation of the Human Rights Act (1998) are considered, although the book was published shortly before the act came into force and discussion of its impact is inevitably speculative.

For the most part, the book is easy to read, but there are some long and complex sentences which I had to tackle several times before appreciating the meaning; it then became clear that the sentences had been constructed deliberately in a rather convoluted way to convey the message in the most succinct and unambiguous manner. Dr Branthwaite's dual qualifications as a physician and a barrister ensure that she does not deviate into areas of the law which are irrelevant to doctors, and this is why the book is comprehensive and immensely informative, yet brief.

I have only two minor criticisms. The first is that, although Dr Branthwaite indicates that, in relation to homicide, 'undue vulnerability of the victim (the 'eggshell skull' rule) does not exonerate the perpetrator', she does not make it clear that the same principle generally applies in civil law. The second is that there is no discussion of the very considerable differences in civil litigation procedures in Scotland and Northern Ireland, although the publishers have made it clear on the back cover that the book focuses on English law.

I learnt a great deal from reading this book. However, two aspects of the law which have always mystified me remain enigmatic.

The first is my quest for a logical explanation of the way in which the multiplier is calculated to estimate the number of years over which loss or expense of an injured claimant is expected to occur. This is, I am told by solicitors, a calculation which barristers claim that only they can perform, and although Dr Branthwaite has provided a little insight into the mechanism (the number of years is 'offset to allow for accelerated receipt and the uncertainties of predicting an individual's future'), I still have no understanding of the reasons why (in the example provided by Dr Branthwaite) the multiplier for a male claimant aged 20 with a life expectancy of another 55 years is about 21 (assuming a return on investments of 4.5%); however, I now know that a secret set of tables exists somewhere from which this value can be derived, and that barristers probably do not perform the calculation in their head after all.

The second relates to involuntary manslaughter. Among the difficulties which senior judges have recognized in this area is how to define the 'gross negligence' which must be proved for a conviction of involuntary manslaughter by breach of duty; at what point does negligence by a doctor become so serious that it warrants punishment by society? In considering an appeal against conviction in a medical case,[1] Lord Taylor set out four 'states of mind' in the defendant which might properly lead a jury to make a finding of gross negligence. The fourth 'state of mind' was: 'inattention or failure to advert to a serious risk which goes beyond "mere inadvertence" in respect of an obvious and important matter which the defendant's duty demanded he should address'. I had anticipated that Dr Branthwaite might have attempted to explain how 'mere inadvertence' can be defined with more precision than 'gross negligence'. Sadly, I was disappointed. She simply reproduced the words of Lord Taylor. I suspect that, on this point, she is as mystified as I am.

This is an excellent book. I think that Dr Branthwaite has explained everything which is explicable. Every doctor would benefit from reading it.

A. R. Aitkenhead

1 R v Prentice. *Weekly Law Reports* (1993) 3: 937C

The Year in Hypertension: 2000. D.H. Elliott, I.M.C. Connell, G.T. McInnes (editors). Published by Radcliffe Medical Press, Oxford. Pp. 400. Price £49.50. ISBN 0953733904.

This book reviews in an elegant manner 150 articles published between 1997 and 1999. For each paper, the background, interpretation and relevant data are presented and commented on. Articles are grouped in sections and in each of these there is a clear introduction, a short conclusion and additional background references. This is extremely helpful. In turn, sections are grouped together in four parts, each with an overall heading. Part I entitled 'Clinical trials and guidelines' reviews recent trial results, and current guidelines, and describes ongoing trials. The current guidelines section makes it clear how difficult it is to issue guidelines with 'universal' applicability. Maybe the most important message is that, in the long-term, the extent of control of blood pressure must take into consideration associated disorders (i.e. diabetes, coronary heart disease, cerebrovascular

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disease) and risk factors. This may have implications for surgical hypertensive patients, though this is not discussed in any way.

Part II deals with the interface of hypertension and other cardiovascular risk factors, especially diabetes, hypercholesterolaemia, and hormone replacement therapy. Part III deals with emerging concepts and reviews articles on specific gene markers, the role of nitric oxide and superoxides, the role of mineralocorticoids, insulin resistance, hypertension and endothelial function. Part IV addresses the current issues in practice. These include the place of angiotensin II receptor antagonists, 24-h blood pressure assessment, surrogate measures of cardiovascular disease (i.e. left ventricular dysfunction, atheromatous vascular disease, endothelial dysfunction, microalbuminuria) and, finally, cost-effectiveness in cardiovascular therapeutics.

For those interested in hypertension, this book is an incredibly useful source of information based on original articles reviewed and commented on by experts. It is a superb reference 'bank' to broaden our knowledge and understanding of arterial hypertension including the most recent concepts. However, it does not address our concerns about the surgical hypertensive patient and its management.

Pierre Foëx

Critical Care Focus (2) Respiratory Failure. H.F. Galley (editor). Published by BMJ Publishing Group, London. Pp. 63; illustrated. Price £14.95. ISBN 0727914669.

This is a 63 page book, edited by Dr H.F. Galley, which is second in what may well be a series of books of intensive care interest that have been co-ordinated by the Intensive Care Society. The contributions in this volume are based on talks given to the 'State of the Art' meeting organized by the Intensive Care Society in December 1998.

The six aspects of ventilatory management in the intensive care unit addressed in this volume are diverse: none tackle the exact topic of respiratory failure. Some of the contributions are good basic physiology and clinical sense: others are interesting hypotheses and conjecture: one hopes that the reader will be able to distinguish these different ingredients, particularly if required to relay them back to an examiner!

The first chapter is a workmanlike compression of material relating to the physiological effects of mechanical ventilation into 18 pages. The result is a slightly patchy and one-sided but usefully up-to-date review. Unfortunately, extreme compression of some of the topics leads to text that is replete with cover-all phrases that can mislead, and cannot hope to represent the range of evidence and opinion that exists on this important topic. The chapter also suffers from some poor figures, which do not do justice to the original data. This is followed by two short useful reviews, by established experts, one on non-invasive ventilation, which is a topic of gradually increasing importance, and a characteristically helpful and thoughtful review of weaning from ventilatory support by Laurent Brochard. A review of the influence of body position on gas exchange in patients with acute lung injury by Antonio Pesenti shows the sad lag between 'surrogate measures' of gas exchange, which are so easily obtained in studies of this type of treatment, and moves to demonstrate a firm clinical benefit. It ends with the statement that 'a multi-centre study is being undertaken'.

The last two chapters are very 'postgraduate'. Geoff Bellingan presents a rigorous review of experimental evidence on pulmonary fibrosis, and the potential for treatment with steroids, again in the experimental stages but of clear interest to the concerned specialist: this is really state of the art material. The last contribution is based on a previous distinguished lecture by John West. It covers what may at first sight be an esoteric topic, capillary stress failure, and reads less freshly than its predecessor, with only a handful of the references from the last 5 yr. However, although it may be a marginal topic, it is put in context by a discussion, albeit short, of ventilator-induced lung injury, which is one of the real advances of the recent past. Both of these last chapters cover fields where intensive care clinicians should be looking (or could have been directed in 1998) for future research topics in respiratory failure, although the present relevance of these contributions to intensive care practice may in some of these instances have been overtaken by further research.

The book comes with no indication of the intended audience, nor of the remit of the series in general. If it is available as a complete series, then I can see a place for it on the intensive care unit as a source for teaching, and intellectual stimulation. However, I could not recommend the purchase of this single volume for instruction or teaching to intensive care trainees, although intensive care specialists will certainly find interest and value in its pages.

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British Journal of Anaesthesia **86** (1): 159 (2001)

Erratum

Publications on paediatric anaesthesia: a quantitative analysis of publication activity and international recognition (BJA 2000; 85: 556–62)

In regard to the article '*Publications on paediatric anaesthesia: a quantitative analysis of publication activity and international recognition*' we would like to express our regret concerning an error made during the publication process of the manuscript. We failed to reference our detailed analysis of the topics of publications on paediatric anaesthesia, published in the September issue of *Paediatric Anaesthesia* (**10**:549–55 [2000]) in the article published in the *British Journal of Anaesthesia.* The preparation and submission of each original manuscript was done immediately after the respective data analysis was completed during November/December 1999.

The two papers are connected as they share the same basic study sample, i.e. the articles on paediatric anaesthesia from 1993 to 1998 published in international journals referenced in Medline™. Whereas the article in *Paediatric Anaesthesia* reports the detailed analysis of the topics of current publications on paediatric anaesthesia, the more recent work in the *British Journal of Anaesthesia* is focused on the publication patterns of the respective authors and journals, on a comparison of their activity in the international sphere, as well as on the international recognition achieved, i.e. by the calculation of related impact factors.

This completely different focus of the paper published in the *British Journal of Anaesthesia* required us to obtain a large quantity of additional data, e.g. demographic data from various sources as well as impact factors and number of annual publications of the journals analysed, which, together with the related results of our formal analysis, are presented therein.

The authors apologize for any confusion this matter may have caused the readers as well as the members of the Editorial Board of the *British Journal of Anaesthesia.*

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BJA

Extended Guide to Contributors*

This is a revised version of the Extended Guide to Contributors which appeared in the Journal in 1990. It should be read in conjunction with the formal Guide to Contributors (in all issues of the Journal). It is intended to advise contributors on the preparation of manuscripts, particularly those who are preparing manuscripts for the first time.

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Aims of the Journal

The *British Journal of Anaesthesia* publishes original work in all branches of anaesthesia, including the application of basic sciences. In addition, the journal publishes review articles, case reports and reports of new equipment.

Some reasons for difficulty

There are several principal reasons for rejection of papers:

(1) *Poor experimental design or inadequate investigation* (or both). Detailed guidance on this aspect is beyond the scope of the present document but inadequate sample size and/or insufficient power are common faults.

(2) *Bad presentation.* This results from inexperience in writing scientific or clinical reports. Various manifestations of the problem may be combined in one manuscript. These include:

(a) Failure to conform to the accepted layout of a scientific paper (see page 132).

(b) Failure to distinguish between jargon and technical terminology (see appendix).

(c) Excessive verbosity. Most manuscripts may be reduced by at least 30% with advantage.

(d) Unsatisfactory or confusing presentation of data in tables or figures (see pages 135, 136).

(3) *Poor English style and syntax.* Although journals are not sympathetic to this problem in papers from the English-speaking countries, *British Journal of Anaesthesia* has a long tradition of helping authors from other countries. Inevitably, however, the provision of this help causes delay.

(4) *Insufficient material.* Try not to break down studies into the smallest publishable units.

Guidance for the early stages

Before beginning to write, analyse your objectives carefully.

What is the question which you have tried to answer?

What message is to be conveyed?

Do the data and your interpretation of them justify the message?

It is recommended that guidance is obtained from colleagues experienced in research and in writing scientific manuscripts.

Statistical analysis is usually an essential component of the process of assessing the validity and implications of any results presented in a paper. Initial statistical advice should be sought before, rather than after, the data have been collected. Do not use 'recipes' for statistical analysis which you do not understand. Do not use the methods of the professional statistician unless you have a reasonable understanding of what they mean.

Do not assume that *figures* that have been prepared for audiovisual presentation will be suitable for publication in a journal; the dimensions are nearly always unsuitable for the printed page (see below).

Consult recent issues of the *British Journal of Anaesthesia* and try to find a paper which conforms, in general format, to the paper you plan to write.

Please make sure that the *legal considerations* which are noted in the formal Guide to Contributors have been fulfilled. It is important to remember also that the internationally agreed code on the ethics of human experimentation (Helsinki Declaration) should be adhered to. A breach of this code will result in automatic rejection. *It is essential to state that local Institutional Ethics Committee approval and informed patient consent have been obtained, where appropriate.* When studies have been conducted in animals, it is essential to indicate the appropriate Home Office Licence number in the United Kingdom or note that approval has been granted by local Animal Research Committees in other countries.

Submission of manuscripts

British Journal of Anaesthesia participates in a uniform requirement agreement on submission of manuscripts (Inter-

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*Copies of this Extended Guide may be obtained from the Editor-in-Chief's Office.

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national Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to Biomedical Journals. *BMJ* 1988; **296:** 401–405).

Manuscripts must be accompanied by a covering letter signed by all the authors. This should include: (a) Information on prior or duplicate publication or submission elsewhere of *any part* of the work. Please note that it is unethical to submit the same complete work to two journals simultaneously; a clear rejection by an editor is required before submission to a second journal should be considered; (b) a statement of financial or other relationships that might lead to conflict of interests; (c) a statement that the manuscript has been read and approved by all authors; (d) the name, address, telephone number, fax number and email address, if applicable, of the corresponding author who is responsible for communicating with the other authors about revisions and final proofs.

Four copies of each manuscript (including revised texts unless instructed otherwise by an editor) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Please do not staple the manuscript but use a paper clip. Contributors should retain a copy in order to check proofs and in case of loss. Manuscripts should only be submitted on disk when an editor requests it. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. At least one set of figures must be unmounted glossy prints (see below); the other three sets may be photocopies. Annotate photographs as necessary.

The typical layout of the manuscript is:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page *one*, etc. Start each section on a separate page. For a Short Communication see page 136.

Title page

A separate page which includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such a 'A new method of scavenging'. Titles in the form of a question, such as 'Is halothane teratogenic?', are often acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. An author's present address, differing from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ($^{1\ 2\ 3}$ etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

A short running title containing not more than 50 characters (including spaces) should be included.

Summary

This should appear on the second sheet and should be presented as *one paragraph* in fewer than 250 words. In many respects the summary is the most important part of the paper because it must give the broad objectives of the enquiry, the principal findings and the essential conclusions. Although the reasons for the investigations may be stated, do not give an extensive review. Give the methods of study, in outline only, together with the principal positive findings and any important negative findings. The main numerical data and probability values should be presented concisely. List the main conclusions, but do not discuss the conclusions and more complex issues. Statements such as 'the significance of these results is discussed' are unhelpful. Only in exceptional circumstances is it appropriate to cite references. Abbreviations, other than the standard abbreviations (see below), should appear in the summary only *after* the term has been defined, and only if the term is to be repeated in the summary. In such circumstances, the term should be given once again in full in the text of the paper, with the abbreviation (in parentheses) following.

Keywords

Three to five keywords should be included on the summary page under the heading Keywords. The system used by the journal follows closely that devised by Greene (see *Key Words in Anesthesiology*, ed. Greene NM, 3rd Edn. Amsterdam: Elsevier, 1988).

Introduction

The introduction should give a *concise* account of the background of the problem and the object of the investigation. It should clearly state the aims of the study. Previous work should be quoted only if it has direct bearing on the present problem. For example, a description and evaluation of a system for scavenging anaesthetic gases from an operating theatre need not include an account of the previous literature of the problems of operating theatre contamination by anaesthetic gases and the many studies of morbidity, etc. which may or may not be associated with such contamination. As a rule, the introduction to a paper should not require more than about 200 words.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

Methods

The title of this section may be 'methods', 'materials and methods' or 'patients and methods'. Under no circumstances should the terms 'patients' and 'materials' be regarded as interchangeable. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). When a manufacturer is unlikely to be known to readers of the journal, the address should be provided also. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Drugs. When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. diazepam 0.1 mg kg^{-1}). Do not confuse drug dose with concentration.

Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Patients. Data on the mean age (range), weight, sex, height, criteria for selection, etc. should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Anaesthesia. Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words:
The patients were premedicated with either morphine 10 mg and atropine 0.6 mg (group A) or diazepam 10 mg (group B), both given 1 h before operation. Anaesthesia was induced with thiopental [give rate of injection where - appropriate], in a dose sufficient to abolish the eyelash reflex. Succinylcholine 80 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with halothane 0.5–1.0% and nitrous oxide 60% in oxygen, the patient breathing spontaneously from a Magill system. A similar description should be used for animal anaesthesia.

Statistical analysis. Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value. If appropriate a power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change.

Additional guidance on statistics may be obtained from Guidelines for Statistical Reporting in Articles for Medical Journals (Bailar JC, Mosteller F. *Annals of Internal Medicine* 1988; **108:** 266–273).

Results

Description of experimental results should be concise. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. It is not usually necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. The editor has the right to request sighting of the original data collected. As a rule, the following general approach should be adopted:

(1) Prepare all the data in the form of tables.
(2) Decide which data are to be presented in the communication.

(3) Can the essential data be presented succinctly in the text? If not, the essential tables or simplified tables should be prepared.

Tables are important communications and should be accompanied by a legend which makes the table self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

Graphs and histograms based on the results should be considered only in the following circumstances:

(1) where a figure will present the data more clearly than is possible in a table.

(2) when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

For more detailed guidance on the format of presentation of results, the reader is referred to previous issues of the journal. A common example, however, occurs in the case of a comparison of the findings in two groups of patients who have been treated with different drug regimens. The following example that required revision is based on a submitted manuscript, with the permission of the authors:

First draft

There were 43 patients in the pethidine group and 41 in the morphine group. Table 2 shows that the two drug groups were evenly matched in terms of age, weight and duration of operation.

Sixty to ninety minutes after the injection, there was a reduction of anxiety score of 2.9 points in the pethidine group (highly significant $P < 0.001$) and a reduction of 1.3 points in the morphine group (significant $P < 0.01$). The difference in the magnitude of the reduction of anxiety between the two groups was not statistically significant. Both groups showed a further significant reduction to normal in the anxiety rating when tested again 24 hours after the operation.

Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Only 12 out of 43 pethidine patients (28%) could remember all three pictures, while 27 out of 40 morphine patients (68%) were able to recall all three picture cards (Table 3). This indicates a significantly greater incidence of amnesia with pethidine than with morphine ($P < 0.01$) using this test. This persisted for 24 hours in three pethidine and five morphine patients.

Local erythema was present in twelve pethidine patients and in ten morphine patients ninety minutes after injection. This disappeared in the pethidine patients but was still present in the ten morphine patients twenty-four hours after surgery ($P < 0.01$).

Second version

Forty-three patients received pethidine and 41 received morphine. The groups were similar in age, weight and duration of operation (Table 2). Sixty to 90 min after injection there was a mean reduction in the anxiety score of 2.9 after pethidine ($P < 0.001$) and 1.3 after morphine ($P < 0.01$). The difference between the two groups was not significant. Both groups showed a further significant reduction to the normal range when tested 24 h after the operation.

Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before operation. Only 12 of 43 in the pethidine group (28%) could recall all three pictures, compared with 27 of 40 in the morphine group (68%) ($P < 0.01$) (Table 3). This persisted for 24 h in three patients in the pethidine group and five in the morphine group. Ninety minutes after injection, local erythema was present in 12 of the pethidine group and 10 of the morphine group. This was still present 24 h after surgery only in the 10 who had received morphine.

In the results section there should be no attempt at a discussion of the findings.

Discussion

This requires discipline by the writer for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there. The form of a discussion should normally follow this pattern:

(1) Summary of the major findings.

(2) Qualifying remarks in relation to these findings; for example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.

(3) Succinct comparison of the present data and relevant data from previous studies.

(4) Deductions—which may explain important differences between the data of the present study and the data of previous studies.

(5) Conclusions from the present study. The original contribution to knowledge from the present study is stated.

(6) The implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.

Acknowledgements

It is inappropriate to acknowledge routine assistance from nursing or surgical colleagues without which any form of clinical research would not be possible. It is essential to acknowledge all sources of financial assistance and any conflicts of interest.

References

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* and *Index Veterinarius* journals.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically in the reference list and numbered accordingly in both list and text.

References in text, tables and legend should be identified by Arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or ^{5}<space>^{16} for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Papers which carry a different system of reference will be returned to the authors for re-typing. The scope for major printer's errors in attempting to rectify inappropriate schemes is considerable.

References in the text. If it is considered essential to cite names of the authors of a study in the text (in addition to the identifying number), up to three names should be cited (A; B and C; D, E and F). In the case of four or more authors, 'G and colleagues', 'G and co-workers', 'G and others' are acceptable. The expression '*et al.*' is not used in the text.

An informal reference to previous work (Z's study or Y's study) is permissible only in a paragraph which contains the reference cited formally.

Abstracts that are more than three years old should not be used as references.

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Personal communications should be cited in the text as (Brown AB, personal communication, year). Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. This should be provided in writing with the first submission of the manuscript.

Papers which have been submitted *and accepted* for publication should be included in the list, with the phrase 'in press' replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction. Abstracts should also be sent with the original submission.

Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

There should be a *table of references* at the conclusion of the paper, commencing on a new sheet. It should be prepared as follows. The names and initials of more than six authors and/or editors should be abbreviated to three names followed by *et al.*

A maximum of 30 references is allowed for an original article and 10 for a short communication.

Journals.

Names and initials of six authors (if more than six, list three followed by *et al.*), title of paper, abbreviated title of journal, year of publication, volume number, first and any change in last page numbers:

Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987; **59**: 14–23

Monographs.

Name of author and initials, title of book (italics), number of edition, town of origin, publisher, year of publication, first and any change in last page numbers (if relevant):

Moore DC, *Regional Block*, 4th edn. Springfield, Illinois: Charles C Thomas, 1979

Chapter in a book.

The reference for an article forming part of a book should take the form:

Hull CJ. Opioid infusions for the management of post-operative pain. In: Smith G, Covino BG, eds. *Acute Pain.* London: Butterworths, 1985; 155–79

It is a serious error to include in the list of references items which are not accurate. It is essential, therefore, that authors check the accuracy of all references which have been listed. It is important also to check that the references listed do indeed appear in the text and *vice versa.*

Preparation of tables

All tables should be on separate sheets and accompanied by legends. Legends should be informative but brief and not contain information which is more appropriate to Methods. Tables may also be submitted on disk. It is preferable to present the data not in table format, but in normal text, with columns separated only by tabs. The tables should be numbered consecutively using Arabic numerals. Units in which results are expressed should be given in parentheses at the top of each column and not

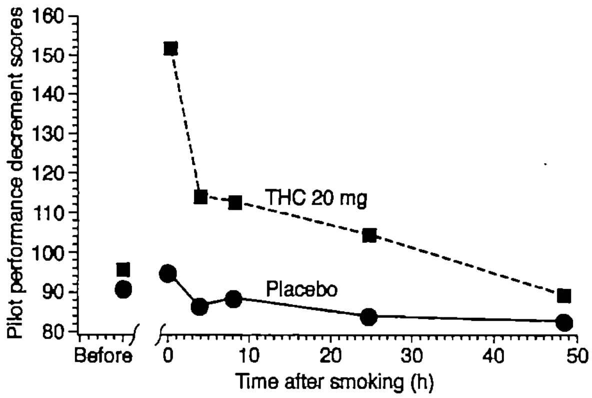

Fig 1 Effect of smoking a cannabis cigarette containing THC 20 mg on pilot performance in flight simulator tasks. Performance on six simulator tasks included in one flight session was standardized to give mean decrement scores; nine pilots performed the tasks under both drug and placebo conditions.[76]

repeated in each line of the table. Ditto signs are not used. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that normally used by the journal; in particular, vertical lines should not be drawn. Please be certain that the data given in tables are correct, as changes at the proof stage are particularly expensive.

Illustrations and figures

Photographs should be unmounted glossy prints and should be protected adequately for mailing. Surfaces should not be marred by clips, pins or heavy writing on the back of the photograph.

Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text and using Arabic numerals. Each figure should be accompanied by a suitable legend.

For publication, illustrations are reduced to single column width see Figure 1 (or in case of particularly complex diagrams, to widths between single and double column).

It should be borne in mind that reduction of figures results in an accompanying reduction of boldness (thickness) of all parts of the figure. It is thus inappropriate to use a variety of boldness of axes, graph lines and lettering in one figure, or to present a figure drawn to a large scale in fine lines and with small, fine lettering. The typewriter line thickness of computer printouts to A4 size is thus to be avoided. The problem of computer-produced diagrams may be obviated by programming the computer to produce a diagram of the same size as that of the final published diagram or, alternatively, to produce lines and lettering of large thickness so that photoreduction results in the appropriate size. Photographs and micrographs should be annotated.

Care should be taken that the labelling of axes does not extend the dimensions of the figure substantially. Avoid suppression of the zero point (the axes may be broken (/ /) if required). (*See also* Units, symbols and abbreviations below).

The foregoing advice, which may not be completely intelligible to many authors, will be understood by a professional illustrator whose advice should be sought in most circumstances. It should be emphasized that the dimensions of a figure prepared for a slide are often unsuitable for reproduction on the printed page. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

Magnifications, especially in photomicrographs, should be indicated on the photograph itself by an unlabelled scale bar which would remain appropriate after reduction. Indicate in the legend the length of the bar.

Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below), as alteration to figures or the re-drawing of them by the publisher is an expensive matter and the cost may have to be borne by the author.

Never send figures or photographs unless a suitable version has been retained on file which may be copied easily in the event of loss.

Units, symbols and abbreviations

British Journal of Anaesthesia, in common with other journals in the UK and many other countries, uses the SI system of units with a few notable exceptions (pH and intravascular and ventilatory pressure measurements, which should be given in units of calibration, e.g. mm Hg, cm H_2O). Blood-gas tensions and the partial pressures in the gas phase should be given in the appropriate SI unit (kPa for kilopascal). It is not intended to give a detailed account of the SI system, the notation of units, symbols and abbreviations in this document. Readers are referred to *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors*, 4th Edn. Baron DN, ed. (1988), published by and available from the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE.

Particular problems have arisen in relation to the *notation* of units which was introduced at the same time as the change to the SI system. Avoid the use of the solidus (/) in favour of various units of the expression set on one line. In the case of expressions 'below the line' superscript $^{-1}$, $^{-2}$, etc. as appropriate is given. Thus for drug dosage we write:

$$\text{mg kg}^{-1}$$

A Guide for Biological and Medical Editors and Authors (Baron, 1988) lists also the abbreviations which may be used by authors without previous definition of their meaning. As noted above, all other abbreviations must be defined, once in the summary and once in the text.

In addition, the 'Pappenheimer' system of abbreviations of respiratory terms (Pappenheimer JR, Comroe JH, Cournand A, Ferguson JKW, Filley GF, Fowler WS, Gray JS, Helmholtz HF, Otis AB, Rahn H, Riley RL. Standardisation of definitions and symbols in respiratory physiology. *Federation Proceedings* 1950; **9:** 602–605) is acceptable without definition.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. This does not include preliminary communications. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and Results; Comment.

Size: Not more than 10 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain corespondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

Further reading for authors

While it is hoped that this extended guide to contributors will be of value to those writing for *British Journal of Anaesthesia*, it should not be regarded as comprehensive instruction for those preparing manuscripts. A number of simple texts and papers have been prepared on this subject and it is essential that the author preparing his first manuscript should avail himself of these. We commend particularly Professor Hugh Dudley's book entitled *The Presentation of Original Work in Medicine and Biology*, published by Churchill Livingstone in 1977. In addition, we recommend that authors should be familiar with Eric Partridge's *Usage and Abusage—A Guide to Good English*, published by Hamish Hamilton in several editions. Sir Ernest Gower's *The Complete Plain Words*, revised by Sir Bruce Fraser, is published by Penguin Books and is a treasure-house of common sense in writing. In the matter of spelling, *British Journal of Anaesthesia* follows the *Shorter Oxford English Dictionary*.

Appendix

Common sources of difficulty include the following:

Blood-gases—specify carbon dioxide, P_{CO_2}, etc.

Blood pressure—avoid this term in favour of arterial pressure, etc. Specify mean, systolic, diastolic.

Case—this should not be regarded as interchangeable with the term 'patient'. An account of the management of a patient may be referred to as a 'case history' or 'case report'.

Chronic bronchitics—avoid this expression when you mean patients with chronic bronchitis.

Data—plural.

Demographics—often used incorrectly to refer to patient characteristics.

Due to—avoid unless in the description of a financial debt. *Because of* and *as a result of* are preferable.

Employed—prefer *used.*

Fall and *Rise*—avoid these expressions which suggest a gravitational influence. *Decrease* or *reduction* and *increase* are preferable.

Groups—avoid expressions such as 'thiopental patients' and 'cholecystectomy patients' in favour of 'patients receiving thiopental' and 'patients undergoing cholecystectomy'. It is permissible, however, to refer to the 'thiopental group' or 'cholecystectomy group'.

High and Low—avoid if you mean large and small.

Incidence—this refers to the proportion of a defined group developing a condition within a stated period. *Frequency* is the number of subjects (expressed usually as a percentage) with a condition. *Prevalence* is frequency at one point in time.

Length (of time or drug effect) —prefer *duration.*

Level—avoid in favour of *concentration.*

Multiple adjectives—avoid using an adjective in apposition to a noun, e.g. 'concentration of sodium' is preferable to 'sodium concentration'.

Postoperatively and *preoperatively*—prefer *after operation* or *before operation.*

Postoperative (preoperative) treatment—acceptable.

Relaxants—avoid in favour of 'neuromuscular blocking drugs'.

Rotameter—note capital letter.

Sacrifice—this is ritualism. Killed is preferable.

Showed—prefer *was present* or *occurred.*

Significant—avoid expressions such as 'highly significant' or 'very highly significant', in favour of *significant* with a probability value in brackets.

Sleep-dose—this is vague. Prefer *a dose sufficient to abolish the eyelash reflex*, etc.

Stable (of measurements) —prefer *unchanged* or *virtually unchanged.*

Teflon—note capital letter

Tendency to change—changed.

It is important to avoid conversational expressions such as:

'the patient was ventilated' (the lungs were ventilated)

'the patient was intubated' (the trachea was intubated)

'the patient was placed on a ventilator' (ventilation was controlled artificially)

'the patient was taken off the ventilator' or 'the patient was weaned from the ventilator' (artificial ventilation was discontinued)

'the patient was extubated' (the tracheal tube was removed).

I S M E T T*

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REGIONAL ANAESTHESIA IN BABIES AND CHILDREN

A joint meeting hosted by **The Royal Hospital for Sick Children, Yorkhill NHS Trust, Glasgow** and the **European Society of Regional Anaesthesia (GB and Ireland)**

Friday 8 June 2001

Beardmore Hotel, Glasgow

SESSIONS 1 & 2 will comprise Presentations followed by Panel Discussion

SESSION 1

- The Pros and Cons of Regional Anaesthesia in Children:
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  - The Hazards .... Bernard Dalens
- New Drugs .... Per Lonnquist

SESSION 2

- Epidural Analgesia
  - Technique .... John Goddard
  - Pharmacology & Physiology .... Eddie Doyle
  - Post-operative Care .... Adrian Lloyd-Thomas

SESSION 3

- WORKSHOPS
  - Chronic Pain
  - Para-vertebral blocks
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  - Head & neck
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1025 - 1055	*Coffee*
1055 - 1120	Anaesthesia and severe Respiratory Disease Dr A Macfie - Western Infirmary, Glasgow
1120 - 1145	The role of central neural blockade Dr G A McLeod - Ninewells Hospital, Dundee
1145 - 1215	Discussion
1215 - 1345	*Lunch*
CHAIRMAN.	Dr N O'Donnell
1345 - 1410	Management of the ruptured aortic aneurysm Dr M Basler - Royal Infirmary, Glasgow
1410 - 1435	Anaesthesia and obesity Dr T Algie - Western Infirmary, Glasgow
1435 - 1450	Discussion
1450 - 1520	*Tea*
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1327 Xenon and Myocardial Reperfusion Injury
1333 Desflurane, Propofol, Sympathetic Nervous System, and Myocardial Stunning
1339 Transcranial Doppler Versus Regional Cerebral Oximetry
1345 Olprinone Effects: Pulmonary Vascular Resistance and Bronchospasm
1351 Mechanisms of Hyperkalemia in Orthotopic Liver Transplantation
1356 Diluted Venous Blood Appears Arterial (Brief Communication)
1358 Nerve Injury During Cardiac Surgery (Review Article)
1370 Bronchial Blocker and Double Lumen Tubes (Case Report)
1372 Epidural Blood Patch, Dural Tear, Thoracotomy (Case Report)

PEDIATRIC ANESTHESIA
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1375 Pulmonary Artery Flow During Fontan Procedures
1381 Work of Breathing in Anesthetized Children
1389 Bronchial Foreign Body Removal (Brief Communication)
1392 Prolonged Duration of Neuromuscular Block with Rapacuronium in the Presence of Sevoflurane (Case Report)
1394 Anesthesia for Fetoscopic Surgery (Case Report)

INTRAVENOUS ANESTHESIA
(Society for Intravenous Anesthesia)

1398 Auditory Response, Bispectral Index, and Propofol

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1404 Dexamethasone and Emesis
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1415 Cataract Surgery and Myocardial Ischemia
1420 Remifentanil, Fentanyl, Cost and Outcome
1426 Month-to-Month Variation in Anesthesia Caseload

CRITICAL CARE AND TRAUMA

1431 Aspiration, Transtracheal Oxygen Insufflation, and CPR

OBSTETRIC ANESTHESIA

1436 Ropivacaine Wound Instillation
1441 Anesthesia for Cesarean Delivery in a Pregnant Woman with Acute Hepatic Failure (Case Report)

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1443 Protection from Opioid Neurotoxicity
1450 Autonomic Dysfunction Secondary to Intracerebral Hemorrhage (Case Report)

REGIONAL ANESTHESIA AND PAIN MEDICINE

1452 Short-Acting Spinal Anesthesia
1457 Intrathecal Ropivacaine
1461 Hypertonic Saline Before Spinal Anesthesia
1466 Hearing Loss After Anesthesia
1473 Continuous Infusion Interscalene Block
1479 Transdermal Ketamine and Postoperative Analgesia
1483 Ketamine and Acute Tolerance to Alfentanil
1489 Toxicity of Ropivacaine and Bupivacaine
1493 Intrathecal Treatment of Spinal Cord Injury Pain
1499 Local Anesthetics Block Tetrodotoxin-Resistant Na+ Channels

GENERAL ARTICLES

1506 Comparison of Jet Ventilation Techniques
1513 Balloon Versus Conventional Laryngoscopy
1520 Reverse Trendelenburg Position and Morbid Obesity
1526 Rocuronium in Chinese and Caucasians
1531 Middle Cerebral Artery Flow During Electroconvulsive Therapy
1537 Pentobarbital-Induced Excitatory Postsynaptic Potentials
1542 Nitrous Oxide and Xenon Increase GABA Response
1550 Accidental Epidural Injection of Vecuronium (Case Report)
1552 Succinylcholine, Hyperkalemia, and Pancreatitis (Case Report)

TECHNICAL COMMUNICATION

1555 Induction With The SiBI™ Connector

1560 LETTERS TO THE EDITOR

1566 BOOK AND MULTIMEDIA REVIEWS

SPA PRECONVENTION ISSUE

SEE INFORMATION INSIDE

ISSN 0003-2999 Volume 91, Number 6, December 2000
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International Journal of Anaesthesia
Volume 86 Number 2 February 2001

EDITORIALS

161 I. Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm
S. J. Howell, J. W. Sear and P. Foex
164 II. Is peri-operative renal dysfunction of no consequence?
M. L. Cittanova
166 III. A breakthrough in the genetic diagnosis of malignant hyperthermia
R. L. Robinson and P. M. Hopkins

CLINICAL INVESTIGATIONS

169 Haemodynamic and renal effects of intravenous enalaprilat during coronary artery bypass graft surgery in patients with ischaemic heart dysfunction
F. Ryckwaert, P. Colson, J. Ribstein, G. Boccara and G. Guillon
176 Is pulmonary resistance constant, within the range of tidal volume ventilation, in patients with ARDS?
G. Mols, V. Kessler, A. Benzing, M. Lichtwarck-Aschoff, K. Geiger and J. Guttmann
183 Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion
J. Vuyk, C. J. Oostwouder, A. A. Vletter, A. G. L. Burm and J. G. Bovill
189 Comparing the effects of stimulation and propofol infusion rate on implicit and explicit memory formation
J. Andrade, L. Englert, C. Harper and N. D. Edwards
196 Absence of memory for intra-operative information during surgery with total intravenous anaesthesia
I. F. Russell and M. Wang
203 Psychomotor recovery in very old patients after total intravenous or balanced anaesthesia for cataract surgery
J. Kubitz, J. Epple, A. Bach, J. Motsch, E. Martin and H. Schmidt
209 EEG bispectral index and hypnotic component of anaesthesia induced by sevoflurane: comparison between children and adults
C.-S. Degoute, C. Macabeo, C. Dubreuil, R. Duclaux and V. Banssillon
213 Sevoflurane EC$_{50}$ and EC$_{95}$ values for laryngeal mask insertion and tracheal intubation in children
R. Aantaa, R. Takala and P. Muittari
217 Effect of common airway manoeuvres on upper airway dimensions and clinical signs in anaesthetized, spontaneously breathing children
A. Reber, R. Paganoni and F. J. Frei
223 Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy
S. G. Soriano, L. J. Sullivan, K. Venkatakrishnan, D. J. Greenblatt and J. A. J. Martyn
230 Epidural analgesia and arterial reconstructive surgery to the leg: effects on fibrinolysis and platelet degranulation
S. A. Bew, A. E. Bryant, J. P. Desborough and G. M. Hall
236 Intrathecal sufentanil and morphine for post-thoracotomy pain relief
N. Mason, R. Gondret, A. Junca and F. Bonnet
241 Spinal anaesthesia with ropivacaine 5 mg ml^{-1} in glucose 10 mg ml^{-1} or 50 mg ml^{-1}
J. B. Whiteside, D. Burke and J. A. W. Wildsmith
245 Rate of injection through Whitacre needles affects distribution of spinal anaesthesia
L. Anderson, J. Walker, C. Brydon and M. G. Serpell

LABORATORY INVESTIGATION

249 Comparison of relaxant effects of propofol on methacholine-induced bronchoconstriction in dogs with and without vagotomy
S. Kabara, K. Hirota, E. Hashiba, H. Yoshioka, T. Kudo, T. Sato and A. Matsuki

REVIEW ARTICLE

254 Anaesthesia and sleep apnoea
J. A. Loadsman and D. R. Hillman

SHORT COMMUNICATIONS

267 Renal effects of inhaled nitric oxide in humans
W. M. Wraight and J. D. Young
269 Can isoflurane mimic ischaemic preconditioning in isolated rat heart?
N. Martini, B. Preckel, V. Thämer and W. Schlack
272 Post-operative recovery: day surgery patients' preferences
K. Jenkins, D. Grady, J. Wong, R. Correa, S. Armanious and F. Chung
275 Attenuation of haemodynamic responses to tracheal intubation by the StyletScope
T. Kitamura, Y. Yamada, M. Chinzei, H. L. Du and K. Hanaoka

CASE REPORTS

278 Unexplained acute severe methaemoglobinaemia in a young adult
M. Falkenhahn, S. Kannan and M. O'Kane
280 Total spinal anaesthesia in association with insertion of a paravertebral catheter
B. Lekhak, C. Bartley, I. D. Conacher and S. M. Nouraei

COMMENTARY

283 Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia
A. Urwyler, T. Deufel, T. McCarthy and S. West for the European Malignant Hyperthermia Group
288 CORRESPONDENCE
295 BOOK REVIEWS
298 ACKNOWLEDGEMENT OF ASSESSORS
301 ERRATA

ABSTRACTS

303P Proceedings of the Anaesthetic Research Society Meeting, London, November 16–17, 2000

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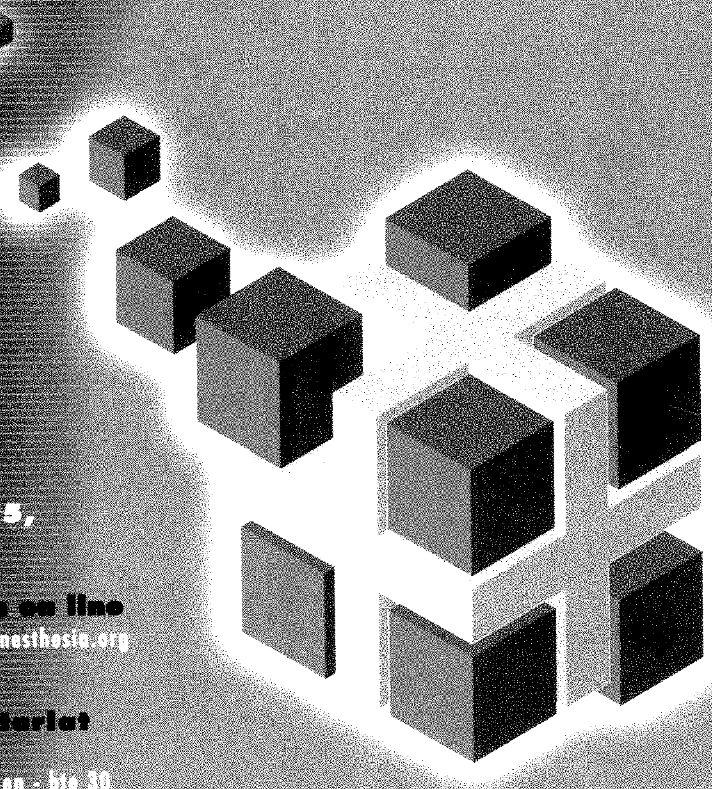

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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

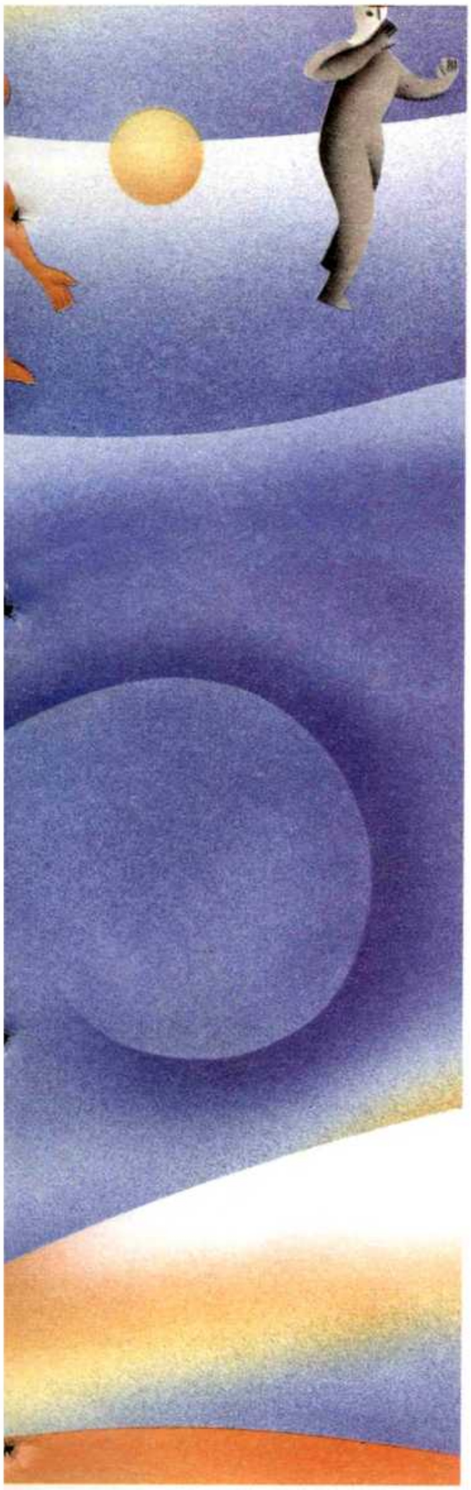
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone. This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1]*

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- Superior GI safety profile compared to conventional NSAIDs – diclofenac, ibuprofen and nabumetone.[2, 3]
- True once-daily therapy – for a wide range of patients.[2]

* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

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Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
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1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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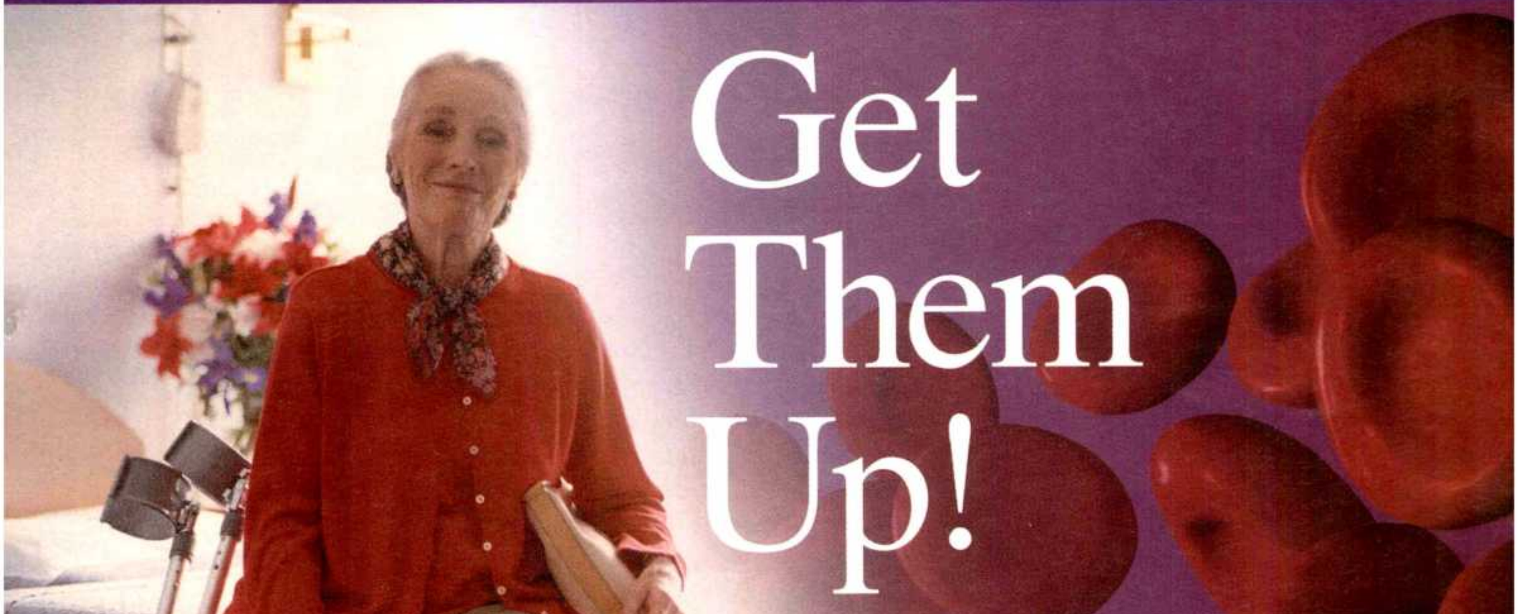

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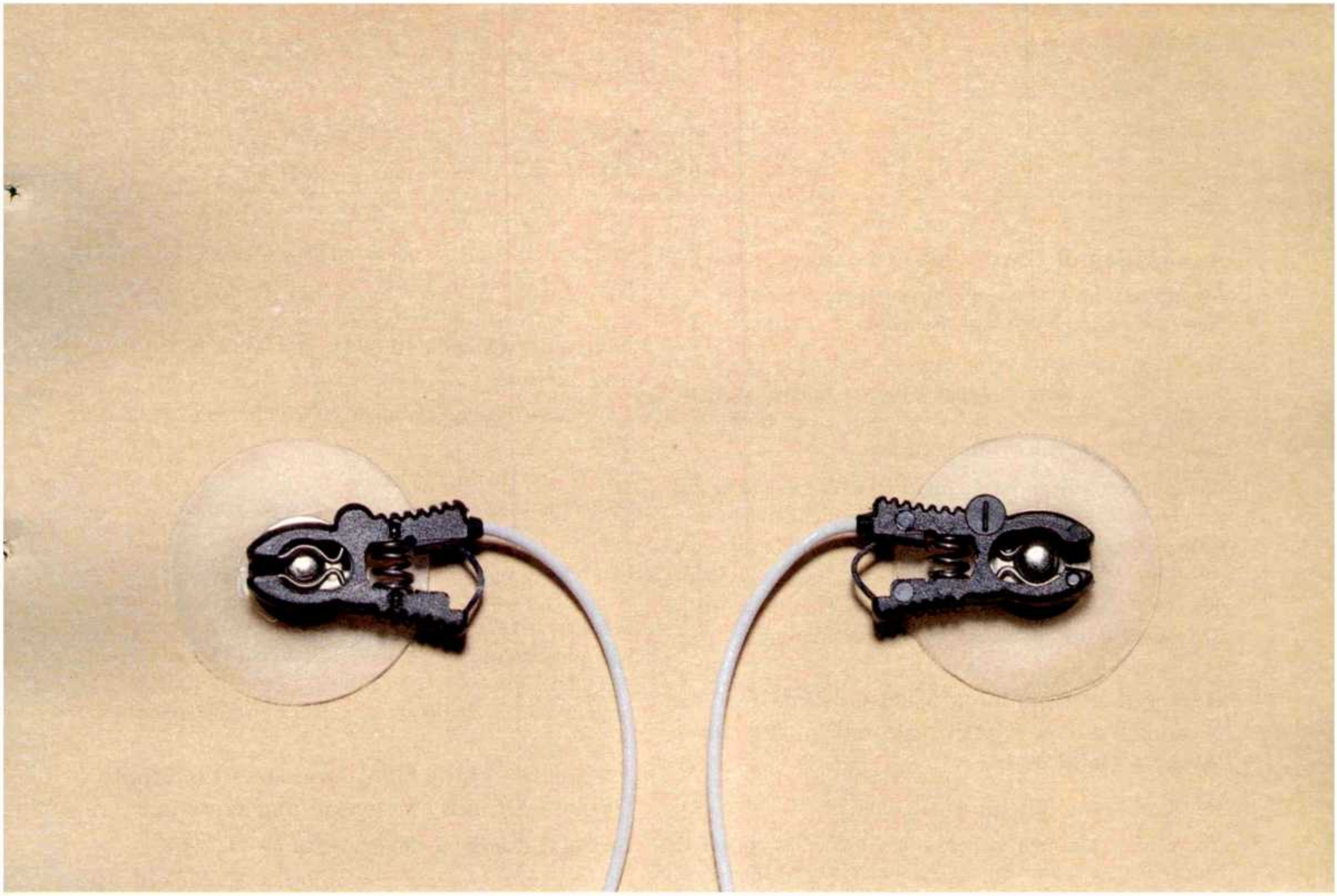

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Editorial Notices

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

Topics include: (i) Management of end-stage respiratory failure; (ii) Mechanical support for the failing heart; (iii) Cardiac transplantation; (iv) Cardiopulmonary transplantation in children; and (v) Re-perfusion injury.

For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

Regional International Meet on Pain Management & XVIth National Society for Study of Pain

Guwahati, India, February 11–13, 2001

The conference, organized by the Assam Society for the Study of Pain under the auspices of ISSP, will be on the theme of 'Reaching out with newer perspectives'.

For further information, please contact: Pain Clinic of North East India, Opp. Bank of Baroda, G.S. Road, Bhangagarh, Guwahati 781005, India. Tel: +91 361 548191; Fax: +91 361 511927; E-mail: issp2001@usa.net

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, March 23, May 4, July 6, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

Neuroanaesthesia Society of Great Britain and Ireland

Churchill College, Cambridge, UK, March 29–April 1, 2001

The Neuro Update Course takes place on March 29–30, 2001. The NAS meeting 2001 takes place March 31–April 1, 2001

For further information on the meeting please visit our website: www.nas.dundee.ac.uk or contact: Conference Secretary (NAS 2001), Department of Anaesthesia, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. Tel: +44 1223 217897; Fax: +44 1223 217223; E-mail: christine.butler@msexc.addenbrookes.anglox.nhs.uk

Advances in Objective Assessment of Hand/ Upper Extremity Function and Outcome

Genval (Brussels), Belgium, April 20–21, 2001

For further information please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail:fschuind@ulb.ac.be

Combined Scientific Meeting (CSM 2001) of The Australian and New Zealand College of Anaesthetists (Faculty of Intensive Care and Faculty of Pain Medicine) and The Hong Kong College of Anaesthesiologists

Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

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Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

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Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, England, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
Tel: 01442 879000. Fax: 01442 870999.

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5th International Conference on Memory, Awareness and Consciousness: Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, NY, June 1–3, 2001

For further information, please contact: (for scientific enquiries) Ruth Reinsel, PhD, Department of Anesthesiology and Critical Care, Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6038; Fax: +1 212 772 8646; E-mail: mac@mskcc.org; website: www.maacc.org or (for other enquiries) Office of Continuing Medical Education, Box 31, Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6754; Fax: +1 212 717 3140; E-mail: cmeinfo@mskcc.org; website: www. mskcc.org

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92; E-mail: SSAI.2001@rito.no
Web site: www.ssai2001.org

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

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ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

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Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

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20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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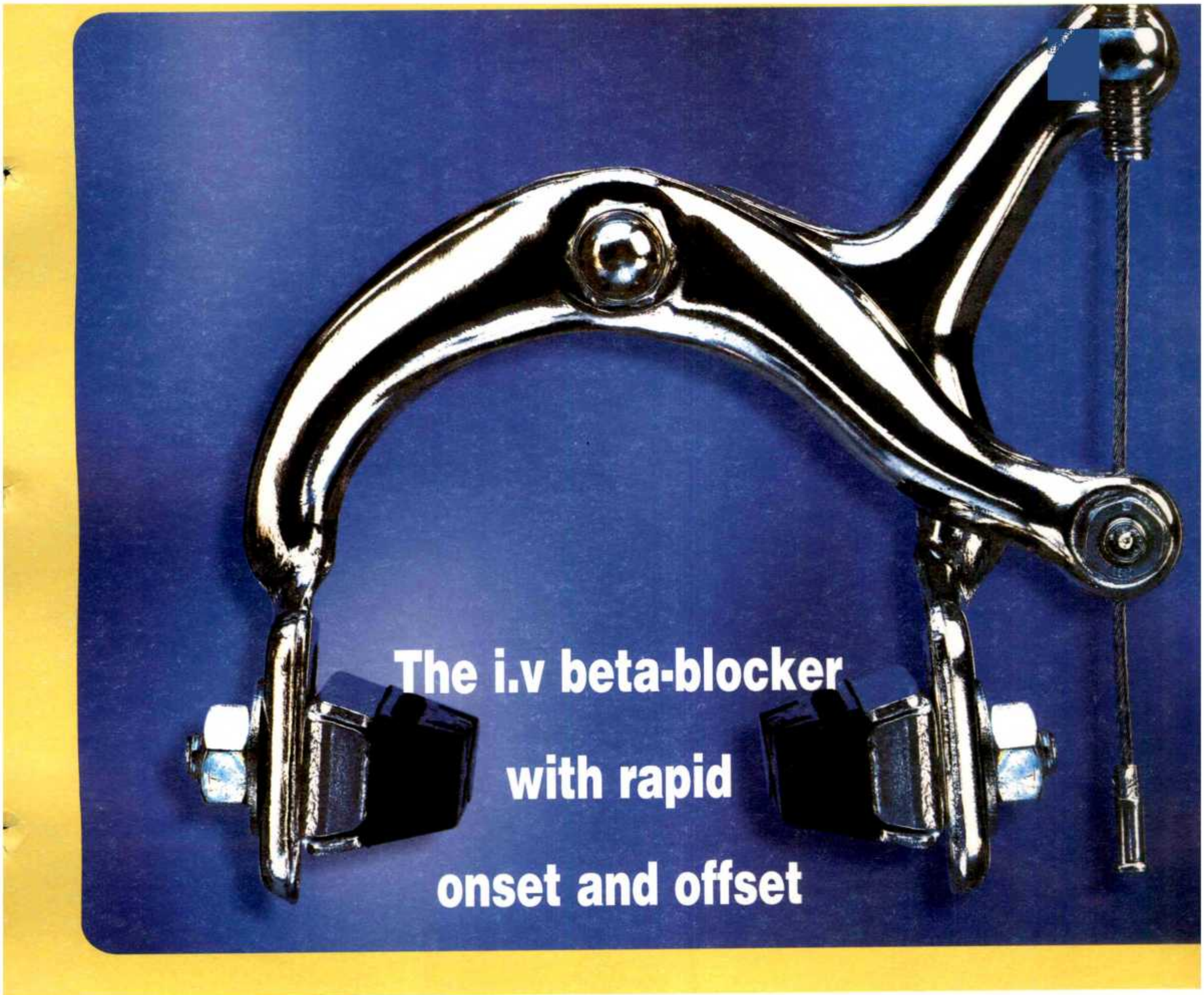

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Editorial I

Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm

Over the past decade, there have been several reports on the use of peri-operative β-adrenoceptor blockade to reduce peak heart rates in response to noxious stimuli or to myocardial ischaemia in patients with arterial hypertension or coronary artery disease.[1–4] Indeed even our sister journal (the *British Journal of Surgery*) has recently published a leading article advocating the widespread use of β-adrenoceptor blockade in all older patients undergoing abdominal surgery, as well as in all patients undergoing vascular surgery.[5] But does the available evidence really support such a stance?

It is proposed that the sympatholytic effects of β-blockade may reduce the incidence of peri-operative cardiac complications. This is certainly plausible. If we believe that peri-operative cardiac events are a result of a supply–demand imbalance in the delivery of oxygen to the myocardium, then any reductions in heart rate and blood pressure produced by β-blockers may minimize such imbalance. A number of studies have shown that peri-operative β-adrenergic blockade reduces the incidence of peri-operative myocardial ischaemia. [1 6 7]

But peri-operative myocardial infarction may not be a result of supply–demand imbalance, but to acute coronary events precipitated by the rupture of an atheromatous plaque in the coronary circulation leading to the occlusion of a coronary artery by thrombus. Thus, Dawood and colleagues found evidence of acute coronary events in the majority of 42 patients who suffered peri-operative myocardial infarction and subsequently underwent post-mortem.[8]

It is well established that β-blockers are effective for the secondary prevention of acute coronary syndromes.[9] It is proposed that the haemodynamic changes induced by β-blockers reduce the shear stress across atheromatous plaques and so reduce the incidence of plaque rupture and consequent acute coronary thrombosis.[10] Alternatively, the beneficial effects of β-blockade may be due to a reduction in the incidence of arrhythmias,[11] either or both of these mechanisms may operate in the peri-operative period. Another possible mechanism whereby benefit could accrue from peri-operative β-adrenergic blockade is a reduction in the neuroendocrine stress response to surgery. However, Zaugg and colleagues were not able to demonstrate such an effect in a population of elderly patients undergoing non-cardiac surgery.[12]

There is certainly evidence from observational studies and non-randomized trials that peri-operative β-blockade reduces the occurrence of peri-operative cardiovascular morbidity, as determined by pressor and chronotropic responses as well as ECG changes associated with ischaemia.[1 6 13 14] However, these are all surrogate measures of cardiac outcome—what the anaesthetist wants to be shown is that a given treatment reduces hard outcome measures (such as cardiac death; Q and non-Q wave infarction; unstable angina; congestive cardiac failure; lethal arrhythmias; renal failure and cerebrovascular accidents). Such outcomes have been addressed in two recent papers.

Mangano and colleagues examined the benefit of peri-operative β-adrenergic blockade in a randomized controlled trial.[15] They studied patients who either had a history of coronary artery disease or had risk factors for coronary artery disease. Patients were allocated to receive either atenolol or placebo before and for 1 week after surgery. Outcomes following discharge from hospital were studied. The authors reported a reduction in overall mortality and combined cardiovascular mortality in the 2 yr following discharge from hospital.

Their study has been criticized on a number of grounds. Patients who were already receiving β-blockers had them discontinued on entry to the study and randomized to β-blocker or placebo. It was felt that this subjected patients who either had or were likely to have coronary artery disease to the hazards of β-blocker withdrawal. Deaths and adverse events in hospital were ignored in the analysis. While the effect of β-adrenergic blockade was significant on survival analysis, it appears that this effect was not significant when outcomes were assessed on 'an intention to treat analysis' that included both in-hospital and long-term adverse events.

These findings of Mangano and colleagues[15] have been further questioned by Leung and Manku.[16] They suggest that the decreased survival may be due not to lack of

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treatment with atenolol but to the high incidence of diabetes mellitus (32%) among the patients studied. Thus, on balance this study presents some evidence for benefit from peri-operative β-blockade in intermediate and high-risk patients undergoing major surgery, but is by no means conclusive.

A second, more recent study has examined the benefits of peri-operative β-adrenergic blockade with bisoprolol.[17] Patients presenting for vascular surgery who had inducible wall motion abnormalities on dobutamine stress echocardiography were studied. They were randomized to standard care alone or standard care and peri-operative β-blockade with bisoprolol, which was started prior to admission to hospital and continued for 1 week after surgery. The main outcome measures were death and cardiac events in hospital. A clear benefit from bisoprolol was demonstrated. Non-fatal myocardial infarction occurred in nine patients given standard care only (17%) and in none of those given standard care plus bisoprolol ($P<0.001$). There were two deaths from cardiac causes in the bisoprolol group (3.4%), as compared with nine in the standard-care group (17%, $P=0.02$). Hence, there was a clear benefit in this study of peri-operative β-adrenergic blockade in a high-risk group of patients. The patients studied were known to have inducible myocardial wall motion abnormalities and the overall cardiac event rate in the standard care group was 34%. On the basis of these findings, it would seem reasonable to suggest that patients who have evidence of inducible myocardial ischaemia on preoperative cardiac stress testing should be given a cardio-selective β-adrenergic blocker in the peri-operative period. Generally, the presence of reversible ischaemia is regarded as an indication for coronary angiography followed, where appropriate, by prophylactic coronary revascularization prior to major surgery. In this study, only a few patients underwent coronary artery bypass surgery; and this may have contributed to a high complication rate in the placebo group.

However in many centres, it would be difficult to identify the subgroup of patients studied by Poldermans and colleagues.[17] Most hospitals do not have the resources to include cardiac stress testing in the preparation of patients for major surgery. Where such testing is available, it is often only used routinely in patients who are to undergo surgery of the thoracic or abdominal aorta. When such testing is used, a significant proportion of patients who have an explicit history of cardiac disease will have a negative test. Such patients are very likely to have non-critical plaques in their coronary arteries. Should these patients receive β-blockers in the peri-operative period, especially in the light of the findings of the post-mortem study of Dawood and colleagues[8] that the majority of acute coronary events leading to peri-operative cardiac death are associated with thrombus formation at previously non-critical plaques?

It seems appropriate that patients who are to undergo major surgery and who have evidence of inducible myocardial ischaemia on stress testing should receive β-adrenergic blockers in the peri-operative period. However, it is not clear that patients presenting for major surgery who have a history of ischaemic heart disease should be given β-blockers on the basis of this history alone. Mangano and colleagues[15] studied patients who either had a history of ischaemic heart disease or who had two or more cardiac risk factors. Thus, many of the patients in their study will have been subject to intermediate rather than high risk of adverse cardiac events. The flaws in their study have already been described and lead one to suggest their study was inconclusive. Although it seems likely that peri-operative β-adrenergic blockade would be of benefit in intermediate risk patients, the case remains unproven. There is an incidence of peri-operative myocardial infarction in older patients who have no previous history of ischaemic heart disease and who undergo major surgery. If the risks of peri-operative β-adrenergic blockade are low, there may be a case for giving β-blockers to all patients over a certain age in whom they are not contra-indicated and who are to undergo elective major surgery. However, there are no data to support this proposition.

In the non-operative setting, β-blocker therapy for the secondary prevention of myocardial infarction offers the greatest benefit to patients over the age of 60 and patients at a moderate or high risk for reinfarction or cardiac death (for example patients with LV dysfunction or arrhythmias or both).[18]

More recently, Urban and colleagues have examined the use of post-operative prophylactic β-blockade in orthopaedic patients at risk of myocardial ischaemia.[4] The aim was to control the post-operative heart rate to <80 beats min^{-1} with an initial infusion of esmolol and then oral metoprolol. Early post-operative ECG changes associated with ischaemia were reduced during the esmolol infusion. Also, for the next two post-operative days there was no effect on the incidences of post-operative cardiac events (angina, congestive cardiac failure, and/or ECG changes and total serum creatine phosphokinase isoenzyme MB fraction index >3.0) or myocardial infarction.

In all of these papers, the benefits (if any) of peri-operative β-adrenergic blockade have to be quantified and set against any risk of harm. Examining these two key studies more closely, Poldermans and colleagues[17] report a RR (relative risk) for cardiac death of 0.20 (95% CI 0.05–0.88) at 30 days post-operation; while Mangano and colleagues[15] report a RR of 0.36 (0.13–0.96) at 24 months. The corresponding RR values for combined cardiac deaths and cardiovascular events are 0.10 (0.02–0.41) and 0.51 (0.31–0.85), respectively.

It has become clear that modest doses of β-blocker may also yield benefit in heart failure. The HOT study indicated that β-blockers do not lead to a worsening of peripheral vascular disease and, in fact, there was an excess of amputations in the captopril group.[19] The medical setting is different to the peri-operative period in that in the latter there are the cardiovascular effects of anaesthesia and of the stress response to surgery to take into account. The currently available studies suggest that the use of β-blockers in the peri-operative period is not associated with significant risk so long as they are withheld if there is relative bradycardia or hypotension. However, this is based on small studies. In intermediate and low risk patients, a large number of patients may have to be treated to prevent one potential peri-operative myocardial infarction. This may be justified, but only if it is clear that adverse events associated with this strategy are rare.

A particular concern is how long treatment should be continued and the possible adverse effects of stopping β-blockers. In the study of Mangano and colleagues,[15] β-blockers were continued for 7 days or until discharge from hospital, which ever was the sooner. In that reported by Poldermans,[17] β-blockers were continued for 30 days after surgery. Neither study reported any adverse effects from discontinuing β-blockade. However, it is suggested that these drugs should be given to patients who either have, or may have, coronary artery disease. It remains possible that larger studies could report the occurrence of angina or myocardial infarction when β-blockers are withdrawn.

Both randomized controlled trials to date have used cardioselective β-blockers. This seems appropriate. The main considerations here are when should β-blockers be started and what degree of β-blockade is required to provide peri-operative cardiac protection. If the β-blocker is started several days before surgery, as was done in the study reported by Poldermans and colleagues,[17] several half-lives will have elapsed by the start of surgery and it is therefore likely that therapeutic levels will be achieved. However, the duration of preoperative treatment may exceed the duration of the peri-operative period for which cardiac protection is sought. Indeed it is possible that β-blockers will be given to patients in whom it is subsequently decided that surgery is inappropriate. If treatment is to be started at the time of admission for surgery then a much shorter period will be available for therapeutic levels to be achieved. In these circumstances, it would seem sensible to use an agent with a short half-life such as metoprolol. Whichever drug is chosen, the optimal dose remains uncertain. It is not clear what degree of sympathetic blockade is required to offer cardiac protection.

There is some evidence that other sympatholytic therapies, such as thoracic epidural block and treatment with α-2 agonists reduce the incidence of peri-operative myocardial ischaemia.[20] The question arises of whether these treatments should be used together. May we expect cardiac protection from β-blockers in a patient who has received a thoracic epidural? Indeed, will the combined sympatholytic effect of the two treatments produce unacceptable hypotension?

While peri-operative β-blockade may offer a valuable intervention that reduces the incidence of peri-operative cardiac complications, a considerable amount of work is still to be done. Should these drugs only be given to patients at high risk of peri-operative complications, or may they have a place in the management of intermediate and low risk patients undergoing major surgery? Is there an ideal time to initiate β-blockade and for how long should it be continued? Is peri-operative β-blockade of value when other sympatholytic therapies are also being used? β-blockers are useful, but we should not embrace them uncritically.

In contrast to these studies examining the effects of 'acute' administration of β-blocking drugs peri-operatively, our own observational studies in a general surgical population (but including high risk vascular surgical patients) have failed to demonstrate an effect of chronic β-blockade on either peri-operative silent myocardial ischaemia;[21] on cardiac mortality at 30 days;[22] or on cardiac mortality or combined cardiac mortality and cardiovascular complications at 1 year post-operation.[23 24]

Thus, while it is accepted that chronic treatment with β-blockers should be continued throughout the peri-operative period and is well tolerated, the peri-operative introduction of β-blockers and the associated side-effects have not been extensively studied. Moreover those studies to date have been carried out in a high dependency or intensive care environment where adverse effects can be easily detected and corrected. This may not be the case on an ordinary ward. The safety of the deliberate addition of β-blocker shortly before surgery needs to be established.

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Editorial II

Is peri-operative renal dysfunction of no consequence?

Post-operative renal dysfunction has long been considered to be a relatively minor event, since its effect on the immediate prognosis of the patient is not evident. Thus, a transient increase in serum creatinine in the post-operative period was regarded as being of little relevance to clinical outcome. Ronco and Flahault[1] highlighted the impact of cumulative renal injuries from various life events, such as nephrotoxic drugs or peri-operative renal insult, which may ultimately lead to irreversible renal injury. Svensson and colleagues[2] had suggested previously that a post-operative increase in serum creatinine of above 180 μmol litre^{-1}, frequently considered as negligible, was associated with an increase in late mortality from 30% to 50% 5 yr after major aortic surgery. Moreover, a recent study by Chertow and colleagues[3] has demonstrated clearly that post-operative acute renal failure, albeit transient, is a risk factor for early mortality following cardiac surgery, even after adjustment for comorbidity and post-operative complications. This large study, which included 42 773 patients, conclusively proved that there is an independent association between post-operative acute renal failure and mortality: dialysis, even if transient, was associated with a 27-fold increase in the odds of death. This contradicts the widely held opinion that acute renal failure is simply a marker of comorbidity.[3] The potential for cumulative small renal insults to lead to irreversible renal failure, and the increase in post-operative mortality due to renal failure (at least in some situations), clearly indicates that post-operative renal failure, even if transient, should be of major concern to the anaesthetist.

Numerous tests have been proposed to assess perioperative renal function but none is ideal.[4] The easiest technique is to record the requirements for dialysis. The advantages of this method lie in its simplicity and objectivity, and the possibility of collecting data from large cohorts, as in the study of Chertow and colleagues.[3] The problem with this technique is its inability to detect lesser degrees of post-operative renal dysfunction, since it only detects a glomerular filtration rate (GFR) of less than approximately 10 ml min^{-1} and thus cannot be recommended to identify moderate renal dysfunction.

An increase in serum creatinine is routinely used to detect perioperative renal impairment and most studies of post-operative renal function have used this variable.[5] However, this technique suffers also from a lack of sensitivity. GFR could be reduced by 50–70% without leading to an increase in serum creatinine concentration because the decrease in glomerular filtration of creatinine is balanced by increased creatinine secretion by cells in the proximal tubule cells. Also, serum creatinine is affected by a number of extrarenal variables, especially in the post-operative period.[6 7] These include fluid loading and the resultant dilution, variable muscle mass and a high metabolic rate, all of which may contribute to misleading information.[4 6 7] Although changes in creatinine and urea are widely used for post-operative renal assessment, they detect only 30% of patients with post-operative renal impairment.[4 8 9] Urinary volume has been proposed as an alternative measure, but is unreliable[10] because oliguria may result also from hypovolaemia or altered concentrations of hormones.

On the other hand, some variables identify a renal abnormality but cannot be used to diagnose renal impairment. Free water clearance, urinary sodium excretion or renal blood flow inform us about renal function but none of them may be used in isolation to define post-operative renal dysfunction. In fact, the strict definition of acute renal failure is a decline in GFR and consequently a retention of nitrogenous waste products such as blood urea nitrogen and creatinine.[7] Since the definition of renal insufficiency is a decrease in GFR, definition of post-operative renal dysfunction should be based on measurement of GFR, the gold standard for which is inulin clearance. Inulin was the first substance to meet the criteria of an ideal filtration marker—it is freely filterable, non-toxic, pharmacologically inert and neither reabsorbed nor secreted—but it is impractical to use because it must be given by constant infusion.[11] Radioactive markers have been proposed because they require only a single infusion to evaluate GFR. The most widely used compounds are [^{99}Tc]DTPA, ^{125}I-labelled iothalamate and [^{51}Cr]EDTA. Methods using labelled agents cannot be recommended for routine use, except when the number of samples is small, because they are invasive and costly. Iodinated contrast agents have been proposed more recently, notably iohexol (omnipaque), whose clearance is well correlated with inulin clearance.[12]

Creatinine clearance has long been used to assess the ability of the glomeruli to filter creatinine. However, the limitations of creatinine clearance in assessing GFR are well recognized, especially in the post-operative period. The main problems with the technique are overestimation of GFR because of tubular secretion[13–15] and the need to measure the urine volume accurately. Some authors[13 16] have compared a 24 h collection with a 2 h collection to assess GFR. These studies have demonstrated that in critically ill patients, creatinine clearance obtained from a 2 h collection provides the same information as reliably as a 24 h collection. The decision is a balance between the risk of residual urine produced but not collected, which favours 24 h collection, and the risks of collection errors and disruption by other complementary investigations, which favour 2 h collection.

Creatinine clearance could be theoretically calculated from creatinine concentration without urine collection using the Cockroft formula.[17] This formula can be used only if the patient has a stable serum creatinine concentration[18] and thus cannot be used when serum creatinine is modified by haemodilution. Consequently, the Cockroft formula is useful for screening high renal risk patients in the *pre-operative* period, but cannot be used to calculate *post-operative* creatinine clearance because serum creatinine is often reduced by haemodilution.

One of the questions raised by Ryckwaert and colleagues[19] in this issue of the journal is the usefulness of improving renal perfusion, and the link between renal blood flow or renal plasma flow and GFR. There is a complex relationship between renal blood flow or renal plasma flow and GFR, including autoregulation of GFR and hormonal control. It cannot be assumed that increasing renal plasma flow, as enalaprilat did in the study by Ryckwaert and colleagues,[19] is equivalent to improving renal function. The two variables are connected but there is not a linear relation between them. The increase in effective plasma renal flow is not surprising since it is a fraction of cardiac output, and this was also increased in the study by Ryckwaert and colleagues.[19] The most serious adverse effect of angiotensin-converting-enzyme inhibitors during anesthesia is hypotension, especially on induction.[20] Hypotension may counterbalance the beneficial effect of improving renal perfusion. It should be noted that Ryckwaert and colleagues failed to demonstrate any improvement in GFR when renal plasma flow increased, except immediately after cardiopulmonary bypass.[19] It remains to be determined whether there is an effect of a transient increase in GFR at this time.

In summary, we have to keep in mind the difficulty in assessing renal function in the peri-operative period, because of the difficulty in accurately measuring GFR. In the post-operative period, patients who require dialysis, or whose serum creatinine is increased, have obviously suffered a serious renal insult. However, 60–70% of cases of renal impairments go undetected and these patients may have a poor long-term renal prognosis. This point is an argument for the assessment of pre-operative and post-operative GFR in high-risk patients. For small numbers of samples in clinical research, labelled agents could be used and iodinated contrast agents are promising. The Cockroft formula is useful in stable situations, such as the pre-operative period. In other cases, the best evaluation is provided by creatinine clearance, even if this technique remains imperfect. In the future, one of the main questions for anaesthetists will be renal protection, as it was for cardiac events in the past decade. We have to define high-risk populations, what should be considered as significant renal impairment, and its impact on patients' health and prognosis.

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Editorial III

A breakthrough in the genetic diagnosis of malignant hyperthermia

The goal of a simple non-invasive DNA test for susceptibility to malignant hyperthermia (MH) has remained elusive. Given the complexity of the disorder at the genetic level, inherent with a genetically heterogeneous[1] condition, the initial aim has been to introduce limited DNA testing for some families. This issue contains the first comprehensive description of the circumstances in which limited DNA testing may be introduced.[2] This is in the form of guidelines produced by the European Malignant Hyperthermia Group (EMHG). It is, however, important to appreciate that these guidelines represent a consensus statement and not a validated process. In this editorial we examine the evidence underpinning the guidelines and the steps required for them to be validated.

For the last 30 yr the invasive *in vitro* muscle contracture test (IVCT) has been the only recognized diagnostic tool to assess MH status. A standardized European protocol was published in 1984.[3] Using this assay patients are assigned MH susceptible (MHS), MH normal (MHN) or MH equivocal (MHE) according to the *in vitro* contracture response of viable muscle tissue following exposure to halothane and separately to caffeine. An increase in contracture of 0.2 g at a threshold dose of 2% halothane, caffeine 2 mM is considered a positive test result. The MHE class includes patients who react to only one of the triggering agents used in the test. Thresholds for this testing procedure have been set to avoid potentially dangerous false-negative diagnoses. Consequently, a false-positive rate of approximately 6% has been suggested from IVCT analysis of patients with a low-risk of MH, using the European IVCT protocol.[4] This can create problems for genetic studies when trying to assess the degree of concordance between IVCT phenotype and 'MH' genotype, an exercise essential in the validation of any genetic testing procedure.

A primary aim of the EMHG has been to standardize testing procedures for MH susceptibility to attain consistency between centres offering a screening service.[3] It should be emphasized that the IVC-testing procedure will retain a central role for the diagnosis of MH in the proposed genetic testing strategy and that genetic testing will not be beneficial to all families. Only on confirmation of MH in a family by an IVCT positive result in a suspected index case would it be appropriate to refer a patient for molecular genetic analysis. Confirmation of MH status through genetic analysis could then lead to quicker results for the rest of the kinship, as opposed to the present situation where IVCT is offered to relatives.

In the EMHG guidelines, two types of analyses are proposed for the genetic investigations.[2]

(i) Mutation testing is proposed only for the *RYR1* gene (encoding the sarcoplasmic reticulum calcium release channel) and then only for *RYR1* mutations recognized as 'causative' of MH. Genetic heterogeneity in MH is well documented with potentially five other susceptibility loci reported through linkage analyses of MH pedigrees.[5–8] However, defects in the *RYR1* gene account for a major proportion of MH cases (up to ~80% of families investigated to date[9]). Restriction of genetic testing to the analysis of 'causative' mutations has been primarily in this direction because all *RYR1* mutations reported to date are missense.[10] The pathogenicity of missense mutations must be carefully considered. Often the effect of such substitutions on protein function is minimal if the side chain of the replacing amino acid is similar to the original (conservative substitutions). Replacements where the side chains are different (non-conservative substitutions) are more likely to have some effect on protein function. Evidence to support the involvement of missense mutations in disease is gained: by considering the position of the affected amino acid in the protein e.g. at a functionally relevant site, or at a site which is conserved across species, or between members of a gene family; by the exclusive segregation of the mutation with the trait; by lack of segregation in a normal control population; and ideally by functional characterization in an appropriate assay.

The 15 mutations listed in the genetic testing guidelines occur in the myoplasmic *RYR1* domain at sites shown to be conserved across the RYR genes characterized to date and in RYR functional homologues cloned from other species.[10] Ten of the 15 mutations result in charge/polarity changes of the amino acid side chain. In addition, no reports have described any of the mutations occurring in patient control groups. All 15 have been investigated in functional assays using cultured cells transfected with mutant RYR channels.[11–15] Mutations that were shown to give a higher amplitude of calcium release in response to low concentrations of caffeine and halothane compared to wild-type RYR channel controls in these studies have been defined as 'causative mutations' in the EMHG guidelines. While the data available support a potential pathological role for these mutations in predisposition to MH susceptibility, the non-physiological conditions and small numbers of cells used in these studies, along with the apparent increasing genetic complexity of the disorder favour a more cautious interpretation of their functional significance. On genetic investigation the guidelines dictate that if a 'causative' mutation were identified in a family member, then the individual would be considered susceptible to MH. If no mutation was detected, even if a familial mutation had previously been identified, the patient must be referred for IVC-testing to confirm MH status.

(ii) Assuming an autosomal dominant mode of inheritance, segregation analysis of genetic markers close to the known MHS loci will have a role in genetic testing. This role will be limited compared to that of mutation screening because the approach is dependent upon the characterization of an extended MH pedigree by the IVCT in order to achieve a statistically significant threshold for linkage. The likelihood of genetic linkage is expressed as the log of the odds ratio, or lod score: a lod score of +3.0 (corresponding to odds of 1000:1) is generally considered as sufficient to establish linkage. This approach will have most relevance to families already extensively characterized by the IVCT and in whom no *RYR1* mutation has been found. If a 'high-risk' haplotype can be established within a family, an individual not previously investigated may be considered at risk of MH, on the basis of genetic data alone, if found to carry the 'high-risk' haplotype identified in the other IVCT-MHS cases in the family. As with the application of mutation testing, the EMHG guidelines advise that an individual must be referred for IVC-testing if the 'high-risk' haplotype is not found.

To the uninitiated the guidelines for testing may seem highly conservative—but for good reason. Genetic testing for MH susceptibility is certainly not at the stage where it may be used in replacement of the IVCT. Thus any genetic analyses must be conducted in co-operation with a recognized IVCT centre. The reason for caution is a consequence of reported discordance between IVCT and genetic data in MH families. Examples include IVC-tested MH normal patients carrying an *RYR1* mutation/'high-risk' haplotype and/or IVC-tested MH susceptible patients who do not carry the familial *RYR1* mutation/'high-risk' haplotype. There are several possible explanations for discordance: a false +ve/–ve IVCT result (the way the thresholds were set for the assay suggests that some false positive diagnoses are inevitable); variable penetrance of the mutation detected; or additional genetic factors may be involved in determination of phenotype in a discordant individual. This raises the question as to the appropriateness of the assumed genetic model for the trait.[16]

Until these observations can be more fully explained, the guidelines advise that for predictive diagnosis in families, a conservative approach is appropriate i.e. either the MHS test result of the IVCT, or the presence of the 'high-risk' haplotype/'causative' mutation will be used to infer an MH susceptible phenotype. An MH negative diagnosis must be confirmed by a normal IVCT result. In this way, false-negative diagnoses are minimized but an increase in false-positive diagnoses is possible. Therefore, a current objective for the EMHG must be to substantiate these guidelines for genetic testing. In a retrospective approach, this will involve extensive genetic characterization of families previously investigated by the IVCT. Data generated from such studies will be pivotal for the validation and appropriate revision of the guidelines if necessary, whereupon it may be necessary to revisit diagnoses based on genetic data alone in some patients.

In conclusion, the publication of a group consensus on guidelines for genetic testing for MH susceptibility is welcomed. The literature to date has not clarified directly, or considered how appropriate genetic testing is for this condition. Data from European studies suggests that such a service will benefit many families, reducing the number of individuals that have to undergo the current invasive testing procedure, and allowing those individuals who may not be eligible for IVC-testing (very young/old) to be investigated.

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CLINICAL INVESTIGATIONS

Haemodynamic and renal effects of intravenous enalaprilat during coronary artery bypass graft surgery in patients with ischaemic heart dysfunction[†]

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Renal dysfunction occurring after open heart surgery is multifactorial in origin but activation of the renin–angiotensin system may have a prominent role. Fourteen patients with ischaemic heart dysfunction scheduled for elective coronary artery bypass graft (CABG) surgery were allocated to a treatment group [enalaprilat for 2 days; ACEI (angiotensin-converting enzyme inhibitor) group, n=7] or a control group (n=7). The cardiac index was significantly higher in ACEI-treated patients than in the controls before and after cardiopulmonary bypass (CPB) ($P<0.05$) and on postoperative day 2 ($P<0.05$). The systemic vascular resistance was significantly lower in the ACEI-treated patients than in the controls before and after CPB ($P<0.05$). Renal plasma flow, measured as [^{131}I]orthoiodohippuran clearance ($\mathrm{Cl_H}$), was higher in the ACEI group than in the control group before CPB, as was endogenous creatinine clearance after CPB ($P<0.05$). On post-operative day 7, $\mathrm{Cl_H}$ was significantly higher in the ACEI group than in the control group ($P<0.05$). Plasma renin activity and vasopressin concentration increased in both groups during CPB ($P<0.05$). The study demonstrates that administration of an i.v. ACEI, enalaprilat, improves cardiac output during CABG surgery in patients with ischaemic heart dysfunction. Moreover, renal perfusion was better maintained during surgery, and this effect was sustained up to post-operative day 7.

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Renal dysfunction may occur after open heart surgery. Depending on the definition used for renal dysfunction, 3–30% of patients may develop a transient decline in renal function.[1 2] Acute renal failure, as defined by the need for dialysis, is a rare (3%) but severe complication of cardiac surgery.[3] Moreover, significant resource use results from renal dysfunction-induced care (mortality, intensive care unit stay, total hospital stay).[3]

Renal dysfunction associated with cardiac surgery is multifactorial in origin, but cardiopulmonary bypass (CPB) and peri-operative low-output syndrome, both of which decrease renal perfusion, have a prominent role.[4] Many studies have reported that CPB in patients who undergo cardiac surgery induces an increase in renal vascular resistance and a decrease in renal blood flow and glomerular filtration rate.[5 6] A recent large-scale study demonstrated that congestive heart failure is an independent pre-operative predictor of renal dysfunction.[3] Among the hormones that may adversely affect renal function, the renin–angiotensin system (RAS) has been shown to be involved in CPB-induced renal dysfunction[6] and heart failure-induced renal impairment.[7] Although RAS blockade with an angiotensin-converting enzyme inhibitor (ACEI) may improve renal function during CPB in patients without pre-existing cardiac or renal failure who are undergoing coronary artery bypass graft surgery,[6] little is known about the effect of ACEI in patients with pre-operative heart dysfunction. The present study was undertaken to evaluate the hypothesis that acute administration of an i.v. ACEI, enalaprilat, may improve

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haemodynamic and renal function during coronary artery surgery in patients with pre-operative cardiac dysfunction.

Methods

Patients

After we had obtained institutional ethics committee approval and informed consent, 14 patients (aged 45–76 yr, 13 males) scheduled for elective coronary artery bypass graft surgery (CABG) were included in the study. All had altered global left ventricular function (ejection fraction less than 40%, as estimated by ventriculography) after myocardial infarction (between 1 month and 17 yr previously). Patients with prior renal dysfunction (serum creatinine >160 µmol l^{-1}), with unstable congestive heart failure, with valvular pathology, or chronically treated with ACEI were excluded. Patients were allocated in a randomized double-blind fashion to the treatment group (ACEI group, *n*=7) or to the control group (*n*=7). Patients in the ACEI group received i.v. enalaprilat (Merck Sharp and Dohme Chibret Lab., Paris, France) 1 mg at intervals of 6 h for 2 days, starting at the time of surgical incision (a dose expected to provide more than 90% inhibition of converting enzyme even in patients weighing up to 100 kg). Patients in the control group received a placebo.

Patient management

The patients were given the usual cardiac treatment, consisting of nitrates (*n*=11), β-adrenergic blocking drugs (*n*=7), calcium antagonists (*n*=7), diuretics (*n*=2) or amiodarone (*n*=2). This treatment was maintained until the day before surgery, except that the calcium antagonists were given on the day of surgery to prevent coronary vasospam.

After overnight fasting, each patient received midazolam 5–10 mg i.m. 30 min before induction of anaesthesia. General anaesthesia was induced and maintained with titrated midazolam 0.10–0.15 mg kg^{-1} and fentanyl 3–5 µg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was used to facilitate endotracheal intubation. After tracheal intubation, ventilation was controlled to ensure normal blood gases, using an inspired oxygen concentration of 50% (oxygen–air mixture) before CPB and 100% after CPB. In all patients, a peripheral vein was cannulated before anaesthesia, then radial artery and pulmonary artery catheters were inserted after induction of anaesthesia for the continuous monitoring of mean arterial pressure (MAP), central venous pressure and for the intermittent determination of cardiac output by the thermodilution technique. Before CPB, hypertension and hypotension were defined as an increase and a decrease in MAP of 20% or more from baseline (preinduction MAP) respectively. Hypertension was treated with additional doses of fentanyl 100–200 µg. Hypotension was treated by rapid i.v. administration of lactated Ringer's solution. Phenylephrine (bolus of 250 µg) was permitted when the MAP was equal to or less than 60 mm Hg (severe hypotension).

After cannulation of the aorta and right atrium, CPB was instituted with a membrane oxygenator primed with 1.5 litres of crystalloid solution and the body temperature was cooled to 27–29°C. After aortic clamping, a cardioplegic solution (hyperkalaemic crystalloid solution) was infused into the root of the aorta until the myocardial temperature fell to 15°C or less. A non-pulsatile pump flow rate greater than 1.6 litre min^{-1} m^{-2} was maintained during hypothermia and increased up to 2.2 litre min^{-1} m^{-2} during rewarming. After completion of the surgical procedure and systemic rewarming, patients were weaned from CPB when a rectal temperature of at least 36°C had been reached.

In the intensive care unit, repeated boluses of morphine were used to keep the patient pain-free. Weaning from the ventilator was started during emergence from anaesthesia and when stable haemodynamic variables and normothermia had been maintained for at least 1 h.

Measurements and calculations

Cardiac output was averaged from three consecutive determinations and the cardiac index (CI) was obtained as cardiac output divided by body surface area. The systemic vascular resistance index (SVRi) was calculated by the standard formula (MAP − central venous pressure/CI) (IU m^{-2}). Systemic haemodynamic variables [heart rate, MAP, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), CI, SVRi] were recorded at the following times: after induction of anaesthesia and before surgical incision; at least 30 min after injection of the first dose of enalaprilat or placebo (before CPB); during CPB (at this time, CI equals the indexed PFR); 30 min after the end of CPB; 6 h after the end of CPB and complete rewarming (postoperative day 0); on the morning of postoperative day 1; and on the morning of postoperative day 2.

Arterial blood was sampled before anaesthesia and during each haemodynamic measurement period. Blood was collected in 5-ml polypropylene tubes containing ethylenediaminetetraacetic acid, and after cold centrifugation the decanted plasma was stored frozen until analysis. Radioimmunoassay was used to measure plasma renin activity (PRA) (2 SD–range normal value 0.2–2.7 ng ml^{-1} h^{-1}), arginine vasopressin (AVP) (kit from Bühlmann Laboratories, Allschwil, Switzerland; 2 SD–range normal value 0.8–6.5 pmol l^{-1}) and aldosterone (2 SD–range normal value 6–12 ng 100 ml^{-1}). Hormone concentrations were corrected for the haemodiluting effect of CPB according to the change in haematocrit, i.e. hormone concentration × Hct_b/Hct_d, where Hct_b and Hct_d are the haematocrit values prevailing before and during CPB respectively.

Effective renal plasma flow was estimated by clearance of [^{131}I]orthoiodohippuran (Cl_H). The labelled compound was injected just after induction of anaesthesia as a bolus of 30 μCi $[^{131}I]$orthoiodohippuran. In addition, a continuous infusion of 40 μCi $[^{131}I]$orthoiodohippuran in 30 ml sodium chloride at a rate of 5 ml h^{-1} was administered throughout the peroperative period in order to obtain a stable blood concentration less than 100 μg l^{-1} for $[^{131}I]$orthoiodohippuran.[6 8] The glomerular filtration rate was estimated as endogenous creatinine clearance (Cl_c). After an equilibration period of 45 min, Cl_c and Cl_H were recorded during surgery and before CPB, and during and after CPB. Urine was collected carefully over at least 30 min and blood was sampled in the middle of each collection period. On the postoperative day 7, the protocol of $[^{131}I]$orthoiodohippuran administration was used, but fluid volume loading (sodium chloride 500 ml h^{-1} for 3 h) was used to get substantial urine production and spontaneous micturition, and the measurements were repeated three times before averaging. Cl_c and Cl_H were calculated as (urine concentration/plasma concentration) × urine volume in ml min^{-1}; these data were corrected for standard body surface area (1.73 m^2).

Table 1 Preoperative data and treatment. Mean (SD) (range)

	Control group	**ACEI group**
Preoperative data		
Age (yr)	66.3 (4.2) (59–73)	60.1 (3.6) (45–73)
Weight (kg)	75.6 (12.6) (56–90)	74.1 (16.3) (53–100)
Height (cm)	166.0 (10.1) (156–178)	168.9 (7.8) (150–180)
Body surface area (m^2)	1.80 (0.3) (1.58–2.00)	1.85 (0.2) (1.46–2.27)
Ejection fraction (%)	36.1 (3.6) (30–40)	34.3 (7.5) (22–40)
Diabetes	1/7	2/7
Serum creatinine (μmol l^{-1})	116.8 (23.4) (87–151)	103.1 (12.0) (80–120)
Preoperative treatment		
Diuretics	1/7	1/7
Nitrates	6/7	5/7
Calcium antagonists	3/7	4/7
β-Blockers	3/7	4/7
Amiodarone	2/7	0/7

Table 2 Intraoperative patient characteristics. Mean (SD) or median (range)

	Control group (n=7)	**ACEI group** (n=7)	P
Total dose			
Midazolam (μg kg^{-1})	307.9 (152.1)	383.3 (86.1)	0.28
Fentanyl (μg kg^{-1})	31.7 (7.7)	29.3 (12.4)	0.67
Fluid administration (ml kg^{-1} h^{-1})	9.7 (1.4)	9.7 (4.3)	0.97
Details of surgery			
CPB time (min)	101.6 (17.8)	91.6 (27.8)	0.44
Aortic clamping time (min)	30.9 (10.4)	26.1 (6.8)	0.33
Number of grafts (range)	2.0 (1–3)	2.0 (1–3)	>0.9
CPB temperature (°C)	29.0 (2.1)	27.7 (1.1)	0.17

Data analysis

Data are expressed as mean (SD). We used two-way analysis of variance for between- and within-group comparisons, corrected for repeated measures when appropriate (Bonferroni's correction). Fisher's exact test was used to compare percentages of patients in the two groups. A P value of <0.05 was considered significant.

Results

Patient characteristics

The two groups of patients were similar with regard to physical characteristics, preoperative left ventricular ejection fraction and preoperative treatment (Table 1). In the ACEI group, the median dose of enalaprilat was 16.7 (2.8) μg kg^{-1} each 6 h (range 13.2–22.2 μg kg^{-1}).

The total dose of anaesthetic medications, intravascular fluid administration and details of CABG surgical procedures were similar in the two groups (Table 2).

Haemodynamic effects

MAP and heart rate before induction of anaesthesia were not statistically different between the two groups: for controls and ACEI-treated patients, MAP was 85.9 (15.3) and 92.3 (10.8) mm Hg respectively (P=0.38), and heart rate was 72.1 (17.0) and 70.3 (12.8) beats min^{-1} (P=0.82). Induction of anaesthesia induced severe hypotension (MAP <60 mm Hg) in three patients (two controls and one ACEI-treated patient), which was treated successfully with phenylephrine (250 μg for each patient). Nine patients (including four controls) received additional lactated Ringer's solution (250–500 ml) after induction of anaesthesia. Administration of enalaprilat or placebo did not induce severe hypotension in either group.

In the control group, the haemodynamic variables were not significantly altered during the intraoperative period except for the heart rate, which increased after CPB (P<0.05) (Table 3). In the ACEI group, the CI increased significantly before and after CPB compared with baseline values (P<0.05); therefore, the CI was significantly higher in ACEI-treated patients than in control patients before and after CPB (P<0.05). The SVRi was significantly lower in the ACEI-treated patients than in the control patients before and after CPB (P<0.05) (Table 3). One patient in each group received vasopressor during CPB.

In the intensive care unit, the CI increased in both groups from postoperative day 0 to postoperative day 2 (P<0.05 and P<0.05 in controls and ACEI-treated patients respectively); CI was higher in the ACEI group than in the control group at postoperative day 2 (P<0.05). The SVRi was lower in ACEI-treated patients than in controls at postoperative day 0 (Table 4).

Table 3 Systemic haemodynamic variables after induction of anaesthesia and before surgical incision (Anaesthesia), at least 30 min after injection of the first dose of enalaprilat or placebo (Before CPB), during CPB (CPB) and 30 min after the end of CPB (After CPB). Mean (SD). $^*P<0.05$ *vs* control group; $^{\dagger}P<0.05$ *vs* anaesthesia period. NA=not applicable; UN=unknown; PCWP=pulmonary capillary wedge pressure; CVP=central venous pressure; CI=cardiac index; SVRi=systemic vascular resistance index; Sv_{O_2} = central venous oxygen saturation

Variable	Group	Anaesthesia	Before CPB	CPB	After CPB
MAP (mm Hg)	Control	79.4 (4.4)	97.7 (3.2)	82.6 (5.9)	83.6 (4.1)
	ACEI	74.3 (5.4)	85.9 (6.8)	73.7 (4.7)	79.9 (2.0)
Heart rate (beats min^{-1})	Control	63.4 (5.3)	69.9 (4.5)	NA	91.6 (6.5)†
	ACEI	66.4 (3.1)	67.1(3.6)	NA	84.4 (4.2)†
PCWP (mm Hg)	Control	13.7 (5.8)	16.6 (7.3)	NA	14.0 (4.8)
	ACEI	19.3 (4.7)	14.7 (4.6)	NA	16.0 (3.5)
CVP (mm Hg)	Control	6.0 (1.4)	5.1 (2.7)	NA	7.6 (4.4)
	ACEI	8.3 (4.8)	5.7 (1.5)	NA	9.0 (2.7)
CI (litre min^{-1} m^{-2})	Control	2.0 (0.2)	2.1 (0.1)	2.1 (0.1)	2.3 (0.2)
	ACEI	2.1 (0.1)	2.7 (0.2)*†	2.3 (0.1)	3.0 (0.1)*†
SVRi (IU m^{-2})	Control	37.4 (7.7)	44.9 (2.5)	38.8 (3.6)	34.5 (3.0)
	ACEI	32.4 (7.1)	30.4 (2.5)*	30.3 (1.9)	24.4 (1.5)*
Sv_{O_2} (%)	Control	73.4 (2.6)	69.2 (4.5)	UN	74.0 (4.6)
	ACEI	68.6 (3.1)	77.1 (1.8)	UN	70.7 (4.6)

Table 4 Haemodynamic variables 6 h after the end of CPB and complete rewarming after surgery (post-operative day 0) and on the mornings of postoperative days 1 and 2. Mean (SD). $^*P<0.05$ *vs* control group; $^{\dagger}P<0.05$ *vs* postoperative day 0. PCWP=pulmonary capillary wedge pressure; CVP=central venous pressure; CI=cardiac index; SVRi=systemic vascular resistance index

Variable	Group	Post-operative day		
		0	1	2
MAP (mm Hg)	Control	79.3 (4.1)	82.8 (5.5)	83.2 (5.2)
	ACEI	67.7 (1.8)	78.8 (6.4)	73.3 (6.0)
Heart rate (beats min^{-1})	Control	90.3 (4.9)	83.0 (4.7)	93.8 (9.8)
	ACEI	85.8 (6.4)	86.2 (7.5)	73.0 (7.9)
PCWP (mm Hg)	Control	9.9 (6.8)	11.7 (5.0)	12.7 (4.3)
	ACEI	12.3 (5.8)	17.5 (10.6)	12.7 (4.9)
CVP (mm Hg)	Control	6.9 (4.5)	7.3 (5.0)	8.5 (4.3)
	ACEI	9.7 (3.8)	8.8 (3.2)	11.0 (3.5)
CI (litre min^{-1} m^{-2})	Control	2.2 (0.2)	2.3 (0.2)	2.7 (0.1)†
	ACEI	2.6 (0.1)	3.0 (0.3)	3.6 (0.4)*†
SVRi (IU m^{-2})	Control	34.7 (3.0)	35.7 (5.5)	28.4 (2.7)
	ACEI	23.2 (1.8)*	25.1 (3.9)	18.5 (3.3)

Renal effects

During surgery, the Cl_H was higher in the ACEI group than in the control group before CPB ($P<0.05$) and on post-operative day 7 ($P<0.05$). The Cl_c was significantly higher in the ACEI group than in the control group after CPB ($P<0.05$) (Table 5).

Hormonal changes

In both groups, PRA increased significantly from baseline during CPB ($P<0.05$ in controls and ACEI-treated patients); at this time PRA was significantly higher in ACEI-treated patients than in controls ($P<0.05$) (Table 6). AVP concentration increased in both groups during CPB ($P<0.05$ in controls and ACEI-treated patients); there was no significant difference between groups (Table 6). There was no difference in the plasma concentration of aldosterone between groups, and no significant change was observed within either group (Table 6).

Outcome

One patient in the ACEI group died during the first 24 h after operation, from acute cardiac failure. The need for inotropic support was not statistically different between the two groups. No patient complained of intraoperative awareness.

Discussion

The study demonstrates that i.v. enalaprilat given to patients with altered left ventricular ejection fraction improves cardiac output during surgery. Moreover, i.v. enalaprilat improves renal perfusion during surgery, and this effect is sustained up to the seventh day after surgery.

The doses of enalaprilat used in the present study were expected to suppress circulating levels of angiotensin II: doses of enalaprilat ranging from 10 to 30 μg kg^{-1} produce marked inhibition (>90%) of plasma angiotensin-converting enzyme activity for 6 h.[9] *In vitro* measurements of angiotensin-converting enzyme inhibition or plasma angiotensin II concentration were not done. However, there was indirect but strong evidence of RAS blockade in the ACEI group in the hormonal profile found in this study. PRA increased at the time of CPB in both groups, which suggests stimulation of the RAS. However, PRA was significantly higher in ACEI-treated patients than in controls, which reflects the lack of negative feedback of angiotensin II on renin release.[10]

The RAS is involved in the regulation of blood pressure, and conflicting results have been obtained with the use of ACEI during surgery with regard to haemodynamic stability. ACEIs have been reported to facilitate the incidence of severe hypotension, to improve haemodynamic status or to be without any significant effect.[11 12] ACEIs given

Table 5 Urinary output, effective renal plasma flow as estimated by clearance of [^{131}I]orthoiodohippuran (Cl_H), glomerular filtration rate as estimated by endogenous creatinine clearance (Cl_c) during surgery and before, during and after CPB and on postoperative day 7. Mean (SD). *$P<0.05$ *vs* control group

Variables	Group	Before CPB	CPB	After CPB	Postoperative day 7
Urinary output (ml min^{-1})	Control	0.86 (0.28)	3.65 (1.17)	2.18 (0.75)	5.07 (1.57)
	ACEI	0.77 (0.20)	3.03 (0.62)	3.15 (0.63)	9.54 (1.49)
Cl_H (ml min^{-1} 1.73 m^{-2})	Control	204 (19)	402 (87)	288 (69)	325 (46)
	ACEI	363 (68)*	605 (154)	843 (330)	490 (37)*
Cl_c (ml min^{-1} 1.73 m^{-2})	Control	56.8 (7.9)	62.2 (16.6)	61.7 (11.4)	87.9 (7.7)
	ACEI	82.3 (19.1)	162.9 (46.2)	142.2 (24.5)*	113.8 (10.6)

Table 6 Plasma renin activity (PRA) and plasma concentrations of arginine vasopressin (AVP) and aldosterone before anaesthesia (Baseline), after induction of anaesthesia and before surgical incision (Anaesthesia), at least 30 min after injection of the first dose of enalaprilat or placebo (Before CPB), during CPB (CPB) and 30 min after the end of CPB. Mean (SD). *$P<0.05$ *vs* control group, $^{\dagger}P<0.05$ *vs* baseline period

Variables	Group	Baseline	Anaesthesia	Before CPB	CPB	After CPB
PRA (ng ml^{-1} h^{-1})	CTL	2.3 (1.1)	5.3 (1.5)	5.6 (1.6)	12.2 (3.0)†	6.3 (2.1)
	ACEI	2.6 (0.1)	2.8 (0.3)	17.1 (6.0)	29.7 (5.2)†*	8.8 (3.0)
AVP (pmol l^{-1})	CTL	4.3 (0.7)	9.1 (3.2)	5.7 (0.4)	70.5 (14.8)†	40.5 (12.6)
	ACEI	4.0 (0.7)	4.3 (1.8)	8.1 (1.9)	61.6 (18.4)†	20.7 (3.8)
Aldosterone (ng 100 ml^{-1})	CTL	13.8 (3.3)	19.6 (4.6)	13.4 (4.5)	11.2 (3.8)	10.2 (1.1)
	ACEI	12.4 (3.0)	15.1 (5.7)	9.8 (3.2)	8.7 (2.0)	9.4 (3.3)

preoperatively in hypertensive patients just before surgery increase the incidence of serious hypotension after the induction of anaesthesia.[13] [14] By contrast, the induction of anaesthesia in patients with left ventricle dysfunction after myocardial infarction may cause a significant decrease in blood pressure, but the risk of severe hypotension is not increased by the ACEI treatment.[15] The underlying cardiac pathology is therefore one of the main factors in the haemodynamic instability of patients with decreased sympathetic tone due to anaesthesia and blocked RAS due to ACEI treatment. In the present study, i.v. enalaprilat was administered to patients with ischaemic left ventricular dysfunction but after the induction of anaesthesia. At the time of the peak effect of enalaprilat,[16] there was no significant change in blood pressure; no severe hypotension occurred, so that no vasopressor was required. Similar results were found by Boldt and co-workers when larger doses of enalaprilat (about 40 µg kg^{-1}) were used after induction of anaesthesia in patients with ischaemic heart disease but without left ventricular dysfunction.[17] An action of AVP to prevent a fall in blood pressure when both the sympathetic nervous system and the RAS are blocked has been suggested as a possible compensatory mechanism.[18] [19] Plasma AVP concentration may increase during heart failure, even when sympathetic responsiveness is decreased.[20] In our study, plasma AVP concentration did not change significantly in either group before CPB. The contribution of any vasopressor system in supporting blood pressure in ACEI-treated patients may be further questioned because vascular resistance did not increase significantly: after enalaprilat, systemic vascular resistance was decreased by 3.1%. Just before CPB, ACEI-treated patients had a lower systemic vascular resistance than controls (by 32%) and an increased CI (by 26%); these effects were maintained after CPB and during the first 2 days after surgery. Such an improvement in cardiac output after acute ACEI treatment in patients with cardiac failure has been observed at rest[21] and during episodes of cardiac failure occurring during[22] or after[23] cardiac surgery. The haemodynamic effect was sustained for the period of ACEI treatment, a fact established several years ago.[7] However, the need for vasoconstrictors and inotropes was not increased in the ACEI group. This contrasts with the observation of an increase in vasoconstrictor requirements after chronic ACEI treatment,[24] possibly related to attenuated adrenergic responsiveness,[25] but corroborates the results of a more recent study.[11] On the basis of these results, it appears that the use of ACEI during CABG surgery reduces the risk of haemodynamic instability in patients with left ventricular ischaemic dysfunction.

The haemodynamic improvement probably played a role in the improved renal perfusion found in the ACEI group. Enalaprilat may also have a direct beneficial effect on renal circulation. The vasodilating effect of enalaprilat may indeed be effective at the level of the renal arteries, so as to reduce renal resistance and to increase renal blood flow in heart failure even when non-hypotensive doses of ACEI are used.[26] The lower Cl_c/Cl_H ratio in the enalaprilat-treated group than in controls before and after CPB (before CPB, 22.7 *vs* 27.8%; after CPB, 16.9 *vs* 21.4%) could reflect the preferential vasodilator effect of ACEI on the post-glomerular arteriole. Although no instance of renal failure occurred after operation in either group, the study confirms that RAS may be involved in perioperative renal dysfunction during cardiac surgery.[6] However, the beneficial effect of RAS blockade was observed during and after surgery.

Conversely, the role of AVP remains unclear. Plasma AVP concentrations were within normal limits before CPB but increased strikingly in both groups during CPB. Light anaesthesia may have contributed to a marked increase in stress-related hormones during CPB, but fentanyl administration may have attenuated the AVP response.[27] Although the mean dose of fentanyl was moderate in our study, plasma AVP concentration did not increase before CPB in either group. The marked increase in plasma AVP concentration could not be related to any changes in haemodynamic variables, though even vasoconstriction should be observed at these plasma concentrations.[28] More surprisingly, renal plasma flow (Cl_H), Cl_c and urinary output were not adversely affected by such elevated AVP concentrations. Such a paradoxical effect of AVP at plasma concentrations above the physiological range has been observed previously during CPB.[28 29]

The changes in renal perfusion thus appeared to parallel the improvement in haemodynamic variables in ACEI-treated patients, and this improvement was also observed 5 days after the enalaprilat treatment had been stopped. The ACEI-induced improvement in haemodynamic variables during and for 2 days after surgery may have contributed to the sustained improvement in renal circulation.[30] Many mechanisms can account for a prolonged improvement in myocardial function beyond the period of ACEI treatment, such as myocardial protection during cardiac surgery,[17] improved coronary circulation[31] and better postischaemic contractile function of the heart.[32] In addition to its macrohaemodynamic effects secondary to the blockade of systemic angiotensin II formation, enalaprilat may have interfered with other vasoconstrictive substances, such as endothelin, epinephrine and norepinephrine.[33] Further investigations are required to assess the exact role of enalaprilat in providing sustained renal preservation after cardiac surgery.

The limitations of the present study include the sample size and the difficulty in assessing renal plasma flow and glomerular filtration rate by means of clearance measurements. The study design allowed patients suffering from ischaemic heart failure but not chronically treated with ACEIs to be included in the study. However, in our university hospital, most patients with ischaemic heart failure scheduled for CABG surgery were already being treated with ACEI because of the proven efficacy of ACEI treatment of heart failure.[12] Consequently, only a small number of patients could be included for the period of the study. Though the small sample size of the study may have weakened the power of the statistical analysis, significant results have been found that show the beneficial effect of enalaprilat on haemodynamic variables during the perioperative period and on some aspects of renal function during and after surgery.

Glomerular filtration rate was estimated by endogenous Cl_c, which has been shown to correlate closely with inulin clearance,[34] but the clinical conditions of CABG surgery make the measurements more difficult. The reliability of Cl_H as an indicator of renal blood flow is even more questionable because of inter-individual fluctuations and the uncertainty of hippuran extraction during hypothermic CPB.[35] Accordingly, a large degree of variability was obtained for most Cl_c and Cl_H measurements. However the few statistically significant differences observed between the groups are in favour of renal preservation in the ACEI-treated patients.

In conclusion, the study showed that enalaprilat administered during coronary artery bypass surgery may have improved haemodynamic variables and renal perfusion in patients with ischaemic cardiac dysfunction. Nevertheless, the results obtained in the small number of patients taking part in this study require confirmation.

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Is pulmonary resistance constant, within the range of tidal volume ventilation, in patients with ARDS?

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When managing patients with acute respiratory distress syndrome (ARDS), respiratory system compliance is usually considered first and changes in resistance, although recognized, are neglected. Resistance can change considerably between minimum and maximum lung volume, but is generally assumed to be constant in the tidal volume range (V_T). We measured resistance during tidal ventilation in 16 patients with ARDS or acute lung injury by the slice method and multiple linear regression analysis. Resistance was constant within V_T in only six of 16 patients. In the remaining patients, resistance decreased, increased or showed complex changes. We conclude that resistance within V_T varies considerably from patient to patient and that constant resistance within V_T is not always likely.

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Acute respiratory distress syndrome (ARDS) is associated with considerable changes in respiratory system mechanics.[1] Clinicians are most interested in the elastic properties of the respiratory system; resistance to gas flow is of less interest. Although resistance is volume dependent when large volume ranges are studied, it is often assumed to be constant within the tidal volume range (V_T). This neglect of resistance in ARDS patients may be because resistance is rarely treated, unlike in obstructive pulmonary diseases. We did not consider resistance when we studied volume-dependent changes in compliance within V_T in 16 patients suffering from ARDS or acute lung injury (ALI).[2] We determined resistance data but did not evaluate them, considering them irrelevant to the effect of the ventilator settings. However, volume-dependent resistance could be of interest, so we have now considered changes in resistance within V_T on the basis of the same measurements.

Methods

Patients

We studied 16 consecutive adult patients with ARDS or ALI (defined according to Bernard and colleagues[3]). Compliance measurements from these patients have been reported.[2] We obtained approval from the institutional ethical committee and written informed consent of the patients' relatives. Patients' lungs were ventilated[4] using a Servo 900C ventilator (Siemens-Elema, Solna, Sweden) in the pressure-controlled mode. We used consensus guidelines that have been previously reported in detail.[2] Since the effects of the given ventilator settings were of greatest interest, the settings were not changed and recruitment manoeuvres were not used.

Determination of resistance: volume-dependent R_{slice} and R_{MLR}

In two patients, gas flow rate was measured with a heated pneumotachograph (Fleisch no. 2; Metabo, Epalinges, Switzerland) connected to the endotracheal tube, which was calibrated with a syringe of 1000 (SD 1) ml (calibration syringe 54500460; Jaeger, Würzburg, Germany). A differential pressure transducer (SPS1, Hoffrichter, Schwerin, Germany) was used to determine the flow proportional pressure difference across the pneumotachograph. Airway pressure was measured by a transducer (1210A; ICSensors, Milpitas, CA, USA) previously tested for linearity between −80 and +80 mbar and calibrated using a Revue Thommen calibrator (Waldenburg, Switzerland). Signals were digitized at 100 Hz with 12-bit resolution (SDM863; Burr Brown, Tucson, AZ, USA). In 14 patients a CP-100

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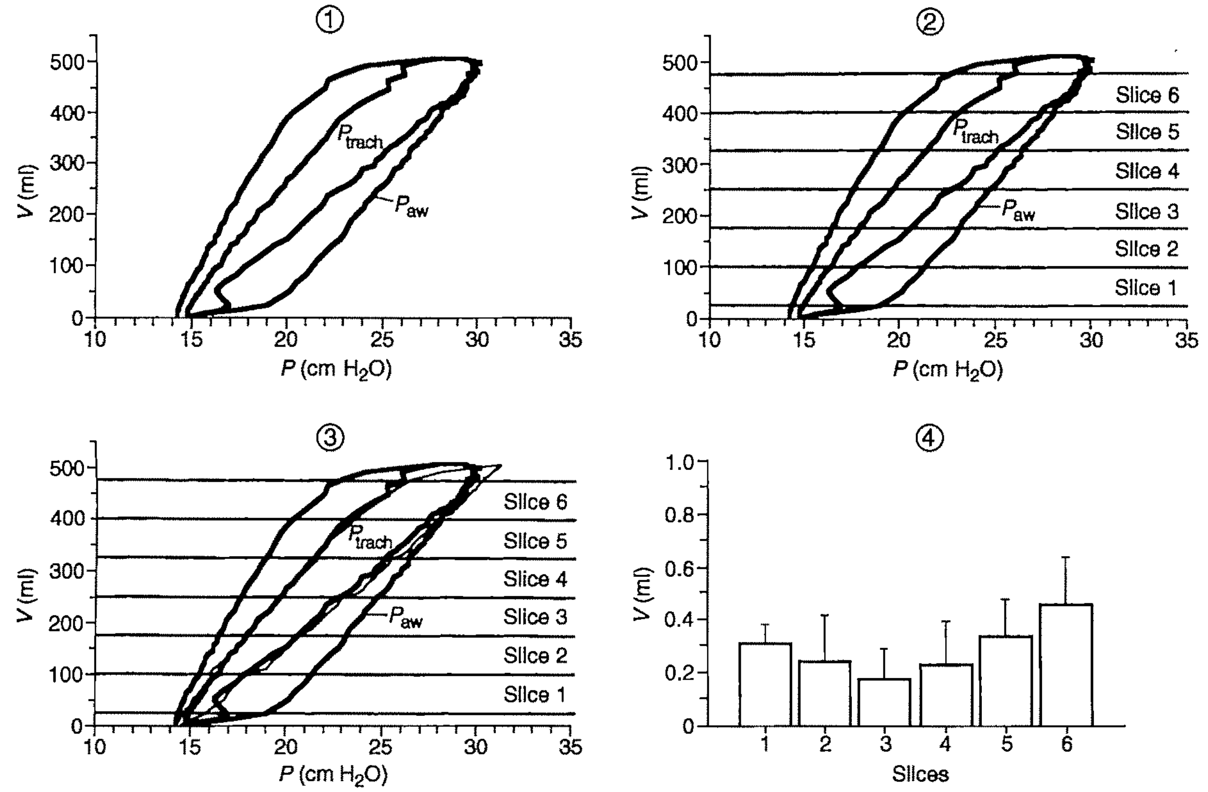

Fig 1 The principle of the slice method involving two steps is shown using an example of a pressure–volume loop. Step 1: the outer loop is based on measured airway pressure (P_{aw}) and volume. Continuous calculation of the flow-dependent pressure drop across the endotracheal tube yields the inner loop, representing tracheal pressure (P_{trach}). Step 2: the loop is divided into six slices of equal volume excluding the uppermost and lowermost 5% of the loop. In each slice, one value of resistance and compliance is calculated based on the simple linear RC model. The resulting R_{slice} and C_{slice} data drawn over volume give the course of these parameters within tidal volume (compare with Figure 2). Two additional steps may be used to verify the quality of the fit. Step 3: the P_{trach}–volume loop (thin line) is reconstructed using calculated respiratory parameters and measured flow and volume. The match of the measured and reconstructed P_{trach}–volume loop give an estimate of the appropriateness of the fit and the model in describing the raw data. Step 4: The absolute difference (mean and SD) between measured and reconstructed P_{trach}–volume-loop (ΔP) is given for each slice.

pulmonary monitor (Bicore Monitoring Systems, Irvine, CA, USA), calibrated according to the manufacturer's instructions, was used for measurements. The raw data were sampled with 50 Hz and passed to a laptop computer. Thereafter, the raw data from both systems were transmitted to a SparcStation 4 workstation (Sun Microsystems, Palo Alto, CA, USA) to calculate volume-dependent respiratory system resistance (and compliance) using the slice method.[5 6]

The slice method uses multiple linear regression (MLR).[7] Rather than using data derived from end-inspiratory and end-expiratory airway occlusion manoeuvres, MLR uses flow, pressure and volume data of the whole breath. If resistance and compliance are assumed to be constant within the tidal volume range, a simple linear model is usually used for this calculation to give average values of resistance and compliance by analysing inspiration and expiration signals obtained during mechanical ventilation without flow interruption. Consequently, the resulting 'dynamic' resistance and compliance values include pressure components associated with stored viscoelastic energy and the effects of inhomogeneous gas distribution.

The slice method enhances standard MLR because changes in respiratory variables over the volume of interest (usually the V_T) can be determined. For this purpose, the V_T is first divided into six volume slices of equal size and MLR is done separately for each slice. The resulting plot of R_{slice} (or C_{slice}) over the volume slices give volume-dependent resistance (or compliance) within V_T.

There are other differences between the slice method and standard MLR. With standard MLR, resistance data are affected by the flow-dependent drop in pressure across the endotracheal tube. With the slice method, this effect is eliminated by continuously calculating tracheal pressure (P_{trach}) before the actual slice calcutions.[8 9] To ensure the accuracy of the P_{trach} calculation in this study, obstruction of the endotracheal tube by secretions or kinking was excluded by suctioning of the airways immediately before the measurements and then monitoring the time constant of passive expiration (τ).[10] The uppermost and lowermost 5% of the pressure–volume loop were excluded from the analysis because of distortions caused by operation of the ventilator valves. Another difference is that the slice method automatically considers intrinsic positive end-expiratory pressure (PEEP).[11]

The principle of the slice method is shown in an example of a pressure–volume loop (Figure 1). Step 1 involves calculation of P_{trach}. The tidal volume is then divided into six slices (step 2) and resistance and compliance are calculated for each slice separately. To assess goodness of fit, the P_{trach}–volume loop is reconstructed using calculated respiratory parameters for each slice and measured flow and volume data. The match of the measured and the reconstructed P_{trach}–volume loop is shown in part 3 of Figure 1. The absolute deviation (mean plus one SD) of the two loops (ΔP) is shown in part 4 (Figure 1). The quality of the fit and the appropriateness of the model are demonstrated by the small ΔP; the fit is best in the middle of V_T. Since the uppermost (and lowermost) 5% of the loop are not adequately described by a model not including inertance, these parts of the loop were excluded from the analysis.

In principle, the course of resistance and compliance within V_T would be better described with a higher (ideally infinite) number of slices, thus increasing the volume resolution of the method. However, for stability of a least-squares fit, a sufficient amount of sampling points per slice is required. Cardiac oscillations transmitted to the measured pressure signal cause considerable noise. Use of six slices gives a good compromise between volume resolution and noise.[5] To reduce noise further, R_{slice} data for 15 breaths were averaged. As well as R_{slice}, we calculated resistance over the entire pressure volume loop (R_{MLR}).[7 12].

We modified the original slice method[5] and did not calculate volume-equidistant data sets from time-equidistant raw data. This computation is time-consuming and requires user intervention, which prevents online calculations of mechanical parameters and hinders clinical application. We therefore no longer use this transformation.[2 6 13] All data are given as mean (SD).

Results

Patient characteristics are presented in Table 1. Patients had both pulmonary and extrapulmonary ARDS/ALI. There was no relationship between resistance (or compliance) data and diagnosis.

The course of R_{slice} within V_T in each patient is shown in Figure 2 (mean (SD) mbar litre^{-1} s). R_{MLR} is drawn as a horizontal line within each plot and its absolute value and SD are given. R_{slice} was constant or almost constant within V_T in patients A, B, E, H, L and P, and it increased in patients D, G, J, K, M and N. A concave pattern of R_{slice} was observed in patients C and I and a convex pattern in patient O. In patient F, R_{slice} decreased within V_T. The C_{MLR} data are given above each graph. The change in C_{slice} within V_T, which has been reported previously,[2] is indicated by the symbol above each graph.

To be sure that the resistance–volume pattern did not merely reflect the flow pattern, the absolute gas flow rate in each slice (mean (SD)) in one representative breath in each patient is shown in Figure 3. As a quality control for the fit, the mean absolute deviation between measured and reconstructed pressure–volume loop is given in Table 2. The mean number of sample points in each slice is given.

Discussion

Resistance often changed within the relatively small tidal volume in ARDS or ALI patients. The course of resistance within V_T varied markedly from patient to patient, with different patterns of R_{slice}. Volume-dependence of resistance in ARDS patients occurs over relatively large volume ranges,[14] but the course of resistance within V_T has not been described before.

Methodological considerations

To determine the course of resistance (and compliance) within V_T, data from the whole breath, i.e. from inspiration and expiration, were used. The resulting mechanical measurements thus represent both phases of the respiratory cycle. Inspiratory and expiratory resistance can be separated by standard (whole-breath) MLR.[7] However, the stability of the fit procedure would have been overstrained by calculation of volume-dependent resistance separately for inspiration and expiration.

The slice method determines resistance as the sum of airway and tissue resistance. The two can be separated with the interrupter technique using sophisticated technical equipment.[15–18] However, airway resistance data obtained by the interrupter technique inevitably contain the resistance of the endotracheal tube. By contrast, resistance data obtained by the slice method are based on calculated P_{trach} after elimination of the resistance of the endotracheal tube.[8 9]

In the slice method, the pressure–volume loop is divided into six slices of equal volume. Potential effects of the gas flow rate on the mechanical parameters are assumed to be negligible. However, the characteristic decelerating flow pattern of pressure-controlled ventilation used here calls this assumption into question. Therefore, we plotted the absolute mean flow rate in each slice for every patient (Figure 3). While slightly differing from patient to patient, the flow rate was distributed over the slices (i.e. the V_T) with a convex pattern. If resistance were to increase with flow rate, a similar pattern would be expected. This pattern was present in patient O and, to a lesser extent, in patients A and H. In all other patients, the course of R_{slice} within V_T was not related to flow values. Consequently, flow has only a minor effect on the course of R_{slice} within V_T. This conclusion supports the findings of Eissa and colleagues,[14] who reported resistance to be grossly independent from the gas flow rate in ARDS patients, although their data were obtained by using the interrupter technique.

Table 1 Patient characteristics and ventilatory parameters. CPR = cardio-pulmonary resuscitation; SIRS = systemic inflammatory response syndrome; MOF = multiple organ failure; HELLP = hypertension, elevated liver enzymes, low platelets. Adapted from reference 2 (p. 1087) with permission from Springer, Heidelberg

Patient	**Age** (yr)	**Gender**	**Diagnosis**	**LIS**[26]	**Survived?**	**PEEP** (mbar)	V_T (ml)	**RR** (min^{-1})
A	31	M	aspiration	2.75	yes	11	750	11
B	18	M	after CPR	1.75	no	12	560	11
C	48	F	pneumonia	2.75	no	11	390	15
D	45	M	pneumonia and sepsis	3	yes	14	690	14
E	24	F	malaria tropica	2.5	yes	10	500	10
F	40	M	stab injury of pericardium and liver	2	yes	10	640	13
G	36	F	HELLP syndrome	3.75	yes	15	500	15
H	30	M	rupture of diaphragm	3	yes	10	290	18
I	26	M	pneumonia and sepsis	3.75	no	14	280	11
J	37	M	pneumonia	3.5	no	13	470	8
K	75	M	pneumonia, SIRS, MOF	2.25	no	8	590	12
L	40	M	blunt chest and multiple trauma	2.75	yes	17	500	14
M	23	F	aspiration	3.5	yes	12	650	13
N	24	M	multiple trauma	3.5	no	14	400	11
O	24	M	blunt chest trauma	3.5	yes	14	250	16
P	42	F	peritonitis	3.75	yes	14	120	21

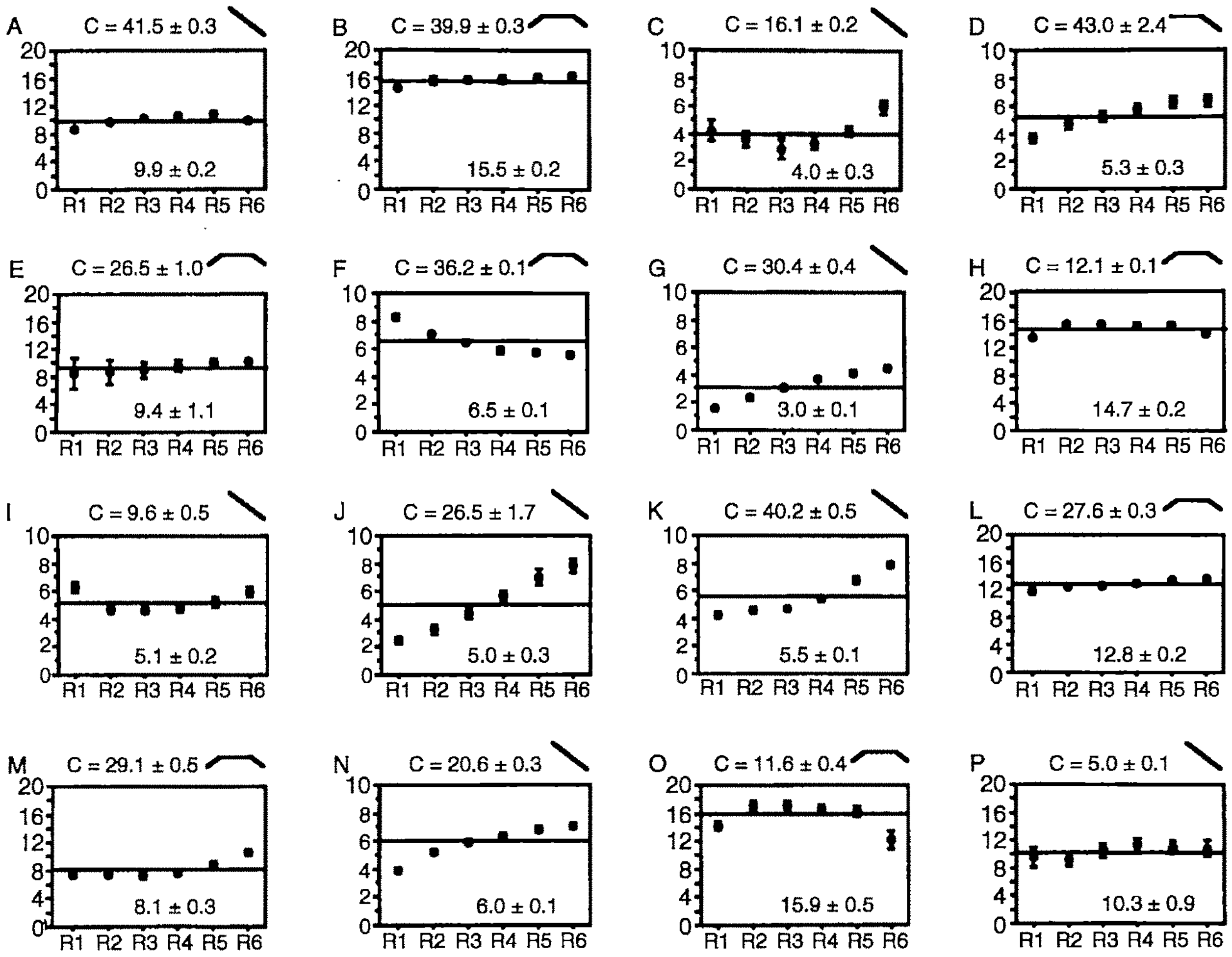

Fig 2 R_{slice} data within V_T (mean and SD, mbar litres^{-1} s; markers for SD often not visible). Note the different scaling on the y-axis. The numbers (R1–6) refer to slices; volume increases from left to right. R_{MLR} of the same breaths are plotted as a straight horizontal line, mean values (with SD) are given. The letters mark the patients studied. C_{MLR} (ml mbar^{-1}) is given above each plot. A symbol showing the course of C_{slice} over volume as previously described[2] is also shown.

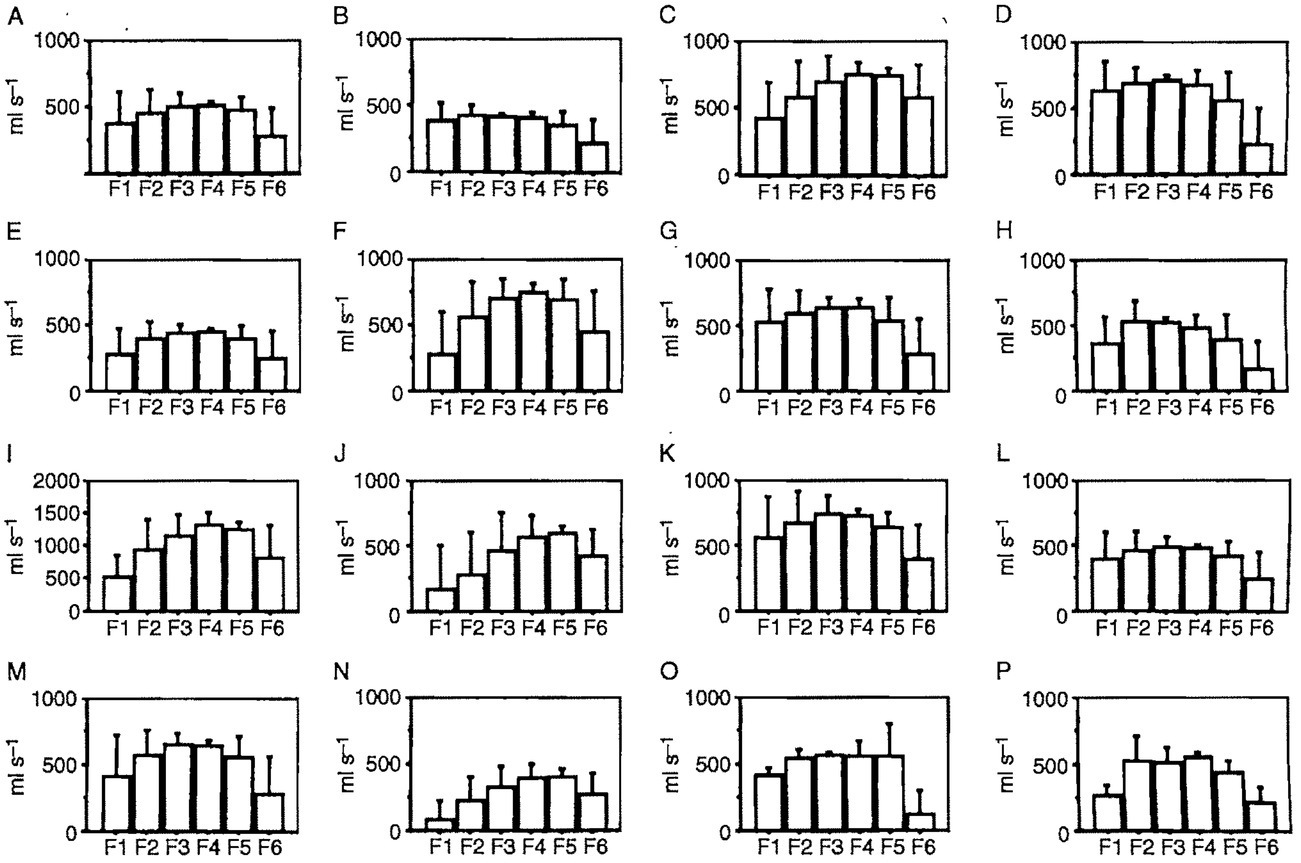

Fig 3 The mean (with SD) flow rate (ml s^{-1}) is shown for each slice in one breath of each patient. The numbers (F1–6) refer to slices; volume increases from left to right. The letters mark the patients studied. Note the different scaling on the y-axis in patient I. The distribution of flow rate over volume (slices) should not be confused with a plot of flow rate over time, which decreases during pressure-controlled ventilation.

Table 2 Quality control of the fit procedure. ΔP=mean absolute difference between original and reconstructed pressure–volume loops (using calculated respiratory parameters for each slice and measured flow and volume data). The number of sample points in each slice was obtained from the first breath, which was recorded in each patient. Data are mean (SD)

	Slice 1	Slice 2	Slice 3	Slice 4	Slice 5	Slice 6
Sample points	31 (25)	21 (11)	18 (11)	17 (8)	19 (8)	34 (14)
ΔP (mbar)	0.8 (0.4)	0.8 (0.4)	0.7 (0.5)	0.9 (0.8)	1.2 (1.2)	1.6 (1.8)

Interpretation of data

Resistance increased considerably in most patients, as often reported in ALI and ARDS patients.[19–21] Classically, resistance should decrease during lung inflation,[22] so a decrease in R_{slice} should also be expected even within the small V_T. Such a pattern of R_{slice} occurred only in patient F, whereas in patient O R_{slice} decreased only at greater lung volume within the tidal volume range. In most of the patients, other patterns of R_{slice} were found. The constant R_{slice} (found in six of 16 patients) is relatively easy to interpret. The studied volume range, i.e. the V_T, may have been too small for a change of resistance to occur.

Other patterns of R_{slice} are more interesting. Several investigators reported an increase of resistance with lung inflation in ALI patients.[20 21 23 24] In these reports, however, the studied volume range was larger. Eissa and colleagues[14] investigated the volume dependence of airway resistance in ARDS patients at different PEEP levels, and hence different lung volumes. Although they studied a volume range that was greater than the tidal volumes studied here, they reported an increase of resistance with lung inflation starting from high PEEP levels (10 or 15 cm H_2O). At lower PEEP levels (0 and 5 cm H_2O) they observed a concave pattern. These data are not directly comparable because they were obtained with the interrupter technique during constant inspiratory flow. How can we interpret an (unexpected) increase in resistance? Longitudinal stretching of airways at high lung volumes could perhaps decrease their cross sectional area, and thus increase resistance.[14]

Our data show no apparent association of PEEP with the course of R_{slice}. This may be because the PEEP was high throughout. Moreover, since larger interindividual differences in lung mechanics exist in ARDS patients, pulmonary overdistension could not be expected at a distinct PEEP level, especially when V_T also differs. However, it may be helpful to consider the C_{slice} data reported previously.[2] A decrease in C_{slice} is interpreted as overdistension. A decreasing C_{slice} coincided with an increasing R_{slice}, at least in the upper slices, in eight of 16 patients (C, D, G, I, J, K, M and N). These data may support the interpretation by Eissa and colleagues[14] of longitudinal airway stretching at high lung volume. As an alternative explanation for the volume-dependent increase in resistance, Pesenti and colleagues[21] suggested an increased tissue resistance caused by inhomogeneity of ventilation at high PEEP levels.

Limitations

This study has two limitations. First, it is an incidental observation. The data were obtained with another end in view, i.e. the analysis of volume-dependent compliance within V_T.[2] The resistance data reported here were not sampled with an *a priori* hypothesis and no plan was followed to investigate the volume dependency of resistance after changes in ventilator settings. Secondly, the resistance data presented here represent the behaviour of the whole respiratory system, containing the lungs and chest wall. While the chest wall's resistance to airflow can be neglected,[20] viscoelastic properties of the chest wall may contribute to the 'dynamic' resistance of the respiratory system. It would only have been possible to separate the resistance of the lung resistance from that of the chest wall by measurement of pleural pressure. It is difficult to measure pleural pressure, so oesophageal pressure is often used as a surrogate. In principle, determination of the lungs' inherent resistance based on measurements of oesophageal pressure would be desirable and this could easily be added to the slice method. However, our purpose in measurement of respiratory mechanics with the slice method in this and other studies[2 6 13] is to develop a concept that will help clinicians to set the ventilator. A non-invasive approach that could be used in standard ventilator equipment is therefore preferable. Measurement of oesophageal pressure is not suited for routine care, because its application is invasive and requires careful adjustment of the catheter's position. Furthermore, oesophageal pressure may not exactly represent pleural pressure, because it is affected by the weight of the mediastinum in the supine position.[25]

Implications and conclusions

Resistance changes considerably, not only in large volume ranges, but also within the relatively small V_T. The method used allows non-invasive and continuous recording of volume-dependent resistance. Clinical benefits for ARDS patients will come only if a thorough explanation of volume-dependent resistance can be derived.

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Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion

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Differences in the pharmacokinetics of propofol between male and female patients during and after continuous infusion have not been described in detail in patients aged 65 yr and older. To increase our insight into the pharmacokinetics of propofol in this patient population and to obtain pharmacokinetic parameters applicable in target controlled infusion (TCI), the pharmacokinetics of propofol during and after continuous infusion were studied in 31 ASA class 1 and 2 patients, aged 65–91 yr, scheduled for general surgery. Patients received propofol 1.5 mg kg^{-1} i.v. in 1 min followed by 7 mg kg^{-1} h^{-1} until skin closure in the presence of a variable rate infusion of alfentanil during oxygen–air ventilation. On the basis of arterial blood samples that were taken up to 24 h post-infusion, the pharmacokinetics of propofol were evaluated in a two-stage manner. Multiple linear regression analysis was used to explore the effect of age, weight, gender and lean body mass as covariates. Gender significantly affected the pharmacokinetics of propofol. V_3, Cl_1 and Cl_2 were significantly different between male and female patients, weight only affected Cl_1. The pharmacokinetic parameters were: V_1=4.88 litre, V_2=24.50 litre, V_3 (litre)=115+147×gender (gender: male=1, female=2), Cl_1 (litre min^{-1})=–0.29+0.022× weight+0.22×gender, Cl_2 (litre min^{-1})=2.84–0.65×gender (male=1, female=2), and Cl_3=0.788 litre min^{-1}.

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Ageing is accompanied by all types of physiological changes and age-related diseases that have implications for the provision of general anaesthesia. Besides changes in the pharmacodynamics of anaesthetic agents that occur with increasing age, age-related changes in body composition, tissue drug binding and tissue perfusion may affect the distribution, redistribution and elimination of anaesthetic agents. These changes may be different between male and female patients.

As the elderly population increases, elderly patients are scheduled for general surgery with increasing frequency. However, rational dosing schemes for propofol in this population are not available. So far, three studies[1–3] have described the pharmacokinetics of propofol during continuous infusion in the elderly. One manuscript described the pharmacokinetics of propofol solely in male patients.[1] The second study determined the pharmacokinetics of propofol in a non-clinical environment in volunteers with only few elderly involved.[2] Lastly, Schüttler and colleagues recently described a population pharmacokinetic parameter set for propofol.[3] However, the small number of elderly patients in this population (10%), the propofol dosing regimen in these patients (some only received a bolus dose), and the short period of time during which concentration–time data of these patients were collected (on average 55 min) leads us to believe that this population pharmacokinetic data set may be less suitable for application in continuous infusion techniques in elderly patients. As propofol is increasingly administered in elderly patients either by manual or target controlled infusion, we studied the pharmacokinetics of propofol in male and female elderly patients during and after termination of a continuous infusion when given as a component of total i.v. anaesthesia for general surgery.

Subjects and methods

With approval of the local Medical Ethics Committee and after obtaining informed consent, 32 patients, ASA I or II,

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aged 65 yr or older (range 65–91 yr), scheduled for general surgery were studied. Patients with known cardiac, pulmonary or renal disease were excluded as were patients consuming more than 20 g of alcohol or smoking more than 10 cigarettes per day.

Patients received temazepam 10 mg orally, 1 h preoperatively. In the operating room, an i.v. cannula was inserted into a large forearm vein for infusion of propofol and alfentanil and a cannula was inserted into a radial artery for the continuous measurement of arterial blood pressure and the collection of blood samples for determination of blood propofol concentrations. The ECG, arterial blood pressure, heart rate, end-tidal carbon dioxide partial pressure and oxyhaemoglobin saturation (Sp_{O_2}, Nellcor N-200, Hayward, CA) were monitored continuously throughout the study.

Before induction of anaesthesia, patients received 500 ml of a colloid solution (Gelofusine). With the patients breathing 100% oxygen, anaesthesia was induced by a manually controlled infusion (Beckton Dickinson, Brézins, France) with a bolus dose of propofol of 1.5 mg kg^{-1} over 1 min followed by a continuous infusion of 7 mg kg^{-1} h^{-1} that was maintained constant until skin closure. When consciousness was lost, vecuronium, 0.1 mg kg^{-1}, was given i.v. and the trachea intubated. The lungs of the patients were then ventilated with oxygen in air (1:2) and ventilation adjusted to maintain the end-tidal carbon dioxide partial pressure between 4–4.5 kPa. In addition, patients received a continuous infusion of alfentanil of 0–50 µg kg^{-1} h^{-1} i.v. that was varied according to the presence or absence of patient responses, and terminated 10 min before skin closure. No response was defined as a systolic blood pressure within a 15% range of the preoperative mean, a heart rate of less than 90 beats min^{-1} in the absence of hypovolaemia, absence of autonomic responses and no movement to surgical stimuli. Post-operative pain relief was provided with rectal paracetamol up to 3 g per 24 h and i.m. methadone up to 0.15 mg kg^{-1} four times daily. Twenty-four hours post-operatively the patients were asked for any recall of events during the study period.

Arterial blood samples of 3 ml for the determination of whole blood propofol concentration were taken at 1, 3, 5, 10, 15, 20, 25, 30 min and then every 15 min after the start of the infusion of propofol, and at 0.5, 1, 2, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 120, 180, 240, 360, 720, 1080 and 1440 min after the termination of the infusion of propofol. The blood samples were transferred into test tubes containing potassium oxalate and stored at 4°C. Propofol concentrations in blood were measured within 12 weeks by reversed-phase high-performance liquid chromatography (HPLC).[4] The detection limit was approximately propofol 40 ng ml^{-1} blood. The coefficient of variation of the HPLC method did not exceed 10% in the concentration range encountered in this study.

The pharmacokinetics of propofol were determined in each patient by fitting two and three compartment models to the concentration–time data with a weighted ($1/y^2$) least squares non-linear regression analysis (software package WinNonLin, Scientific Consulting, Inc., Cary, NC, USA). In a two-stage manner, the simple average pharmacokinetic parameter set was determined. The effect of age, gender, total body weight and lean body mass on the pharmacokinetic parameters was then evaluated by univariate and multivariate linear regression analysis (SPSS 9.0, SPSS Inc USA). Based upon partial *F*-tests ($P<0.05$), successive variables were included. Finally, if more than one covariate was included plausible interaction terms were examined and based upon *F*-tests ($P<0.05$) this term was either included or excluded. Independent covariates were tested for multicollinearity. If the tolerance exceeded 0.5 multicollinearity was considered to be not substantial. The simple (average) model and the final (complex) pharmacokinetic parameter set were retrospectively tested for their clinical value by determining the accuracy with which the parameters predicted the measured blood propofol concentrations in the individual patients.

The performance error (PE) was calculated as:

$$PE = \frac{C_m C_p}{C_p} \times 100,$$

where C_m and C_p are the measured and predicted blood propofol concentrations. Subsequently, the bias and inaccuracy associated with each pharmacokinetic parameter set were assessed by determining the median performance error (MDPE), the median absolute performance error (MDAPE), and the corresponding interquartile ranges (25–75%).

Data are presented as mean (SD), median and range, or percentage, unless stated otherwise. $P<0.05$ was considered as the minimum level of statistical significance.

Results

The concentration–time data of 31 (16 male, 15 female) of the 32 patients that were enrolled in the study were available for evaluation. In one patient, the infusion of propofol was interrupted because of an obstruction of the i.v.-line and the concentration–time data of this patient were not included in the evaluation. No significant differences existed between the male and female patients with respect to age (mean (SD)) (73.3 (6.1) *vs* 72.5 (6.2) yr), weight (75.3 (9.5) *vs* 71.1 (11.1) kg), propofol infusion duration (120.1 (79.8) *vs* 111.0 (44.9) min) or mean alfentanil infusion rate (37.2 (28.2) *vs* 50.4 (21.5) µg kg^{-1} h^{-1}). Surgical procedures included herniotomies, mastectomies, cholecystectomies and minor bowel surgery.

From the 31 patients, a total of 932 blood samples for determination of blood propofol concentrations were taken over a 24 h period. The pharmacokinetics of propofol were

Table 1 The simple (average) and complex (final) pharmacokinetic parameter set (SD) of propofol in the elderly. M, mass (kg); G, gender (male=1, female=2)

	Simple (average) pharmacokinetic parameter set	Complex (final) pharmacokinetic parameter set	R^2	P
V_1 (litre)	4.88 (2.23)	4.88 (2.23)		
V_2 (litre)	24.5 (12.1)	24.5 (12.1)		
V_3 (litre)	334 (197)	115+147*G	0.144	0.035
Cl_1 (litre min^{-1})	1.65 (0.37)	–0.29+0.022 * M+0.22 * G	0.477	0.001
Cl_2 (litre min^{-1})	1.88 (0.83)	2.84–0.65*G	0.155	0.028
Cl_3 (litre min^{-1})	0.788 (0.256)	0.788 (0.256)		

Table 2 The accuracy (median performance error; MDPE) and precision (median absolute performance error; MDAPE) and interquartile ranges of the measured versus predicted propofol concentrations on the basis of the complex pharmacokinetic parameter set of this study and on the basis of those predicted with the use of the pharmacokinetic parameter sets by Dyck and Shafer,[1] Schnider and colleagues[2] and Schüttler and colleagues[3]

	MDPE (25–75%)	MDAPE (25–75%)
This study	1 (–5 to 13%)	18 (14–22%)
Dyck and Shafer[1]	18 (–5 to 26%)	33 (29–37%)
Schnider and colleagues[2]	20 (9–33%)	27 (20–35%)
Schüttler and colleagues[3]	–38 (–53 to –29%)	40 (32–53%)

best described on the basis of a three-compartment model in all patients. Gender significantly affected the pharmacokinetics of propofol. V_3, Cl_1 and Cl_2 were significantly different between male and female patients. In addition, Cl_1 was weight dependent. The simple and final complex pharmacokinetic parameter sets are described in Table 1. The performance of the simple average pharmacokinetic parameter set, as tested retrospectively by computer simulation in the individual patients, showed a reasonable performance (MDPE (25–75%), 2% (–9 to 15%); MDAPE 22% (18–26%)). The addition of the covariates improved the performance as shown by a reduction in both the bias and inaccuracy and their interquartal ranges (MDPE (25–75%), 1% (–5 to 13%); MDAPE 18% (14–22%), Table 2). For the application of the pharmacokinetic parameter set to a target controlled infusion, the performance of the final complex model was determined as well only for the period of propofol infusion: (MDPE (25–75%), 3% (–2 to 13%); MDAPE 14% (11–20%)). The performance of the complex model is illustrated in Fig. 1, which shows the measured and predicted concentration-time data in the patients with the best and worst performances as based on MDPE.

Discussion

Based on empirical findings, the propofol dosage and rate of administration in the elderly generally are reduced to diminish unwanted side effects. To what degree the dosage should be reduced and if gender affects this reduction, however, is not known. This report describes the concentration–time relationship of propofol in elderly female and male patients during and after propofol administration by a standard manually controlled infusion in the presence of a variable-rate infusion of alfentanil during total i.v. anaesthesia for general surgery.

Gender differences in the elderly receiving propofol

In this study, we found that gender affected the pharmacokinetics of propofol in elderly patients. The pharmacokinetic analysis revealed a larger slow peripheral volume of distribution (V_3), a higher metabolic (Cl_1) but a reduced rapid peripheral clearance (Cl_2) in elderly female patients compared with elderly male patients. Previously, Dyck and Shafer[1] only studied male patients, Schüttler and Ihmsen[3] did not find a gender difference in the propofol pharmacokinetics, whereas Schnider and colleagues[2] described that gender of itself did not affect the pharmacokinetics of propofol but, by affecting lean body mass (LBM), influenced the metabolic clearance. The LBM of for instance a 73-yr-old, 75 kg, 180 cm male is 60.2 kg, whereas a female with the same characteristics has a LBM of 54.6 kg. As a consequence, according to Schnider and colleagues[2] the clearance in this elderly male is 1.80 litre min^{-1}compared with 2.18 litre min^{-1} in the elderly female. When elderly male and female patients are given the same propofol infusion scheme the blood propofol concentrations in the female patients will be approximately 10% lower compared to that in the male. These results are based on both the pharmacokinetics of Schnider and colleagues[2] and on the pharmacokinetics reported in this study (Fig. 2). The gender related differences may be explained on the basis of gender related differences in physiological parameters such as cardiac output and amount of body fat. Male patients generally exhibit a higher cardiac output and thus a greater hepatic perfusion compared with females.[6] For a high extraction-ratio drug like propofol, hepatic clearance is strongly correlated to hepatic perfusion and a gender related difference in hepatic perfusion may explain the difference in clearance found in this study. Similarly, the difference in the amount of body fat between elderly male and female patients may be responsible for the greater peripheral slow volume of distribution (V_3) in female compared with male patients in our study. Clinically, these results indicate that in order to assure the same blood propofol concentration in elderly female and male patients, female patients require an approximately 10% higher propofol infusion rate. Furthermore, when female and male patients receive the same infusion scheme, the lower blood propofol concentrations in female patients (Fig. 2) may explain the described difference in speed of recovery between female and male patients.[7] When female patients experience lower blood propofol concentrations compared with male patients during similar propofol infusion schemes, in the presence of a similar pharmacodynamic profile, female patients will regain consciousness more rapidly than male patients.

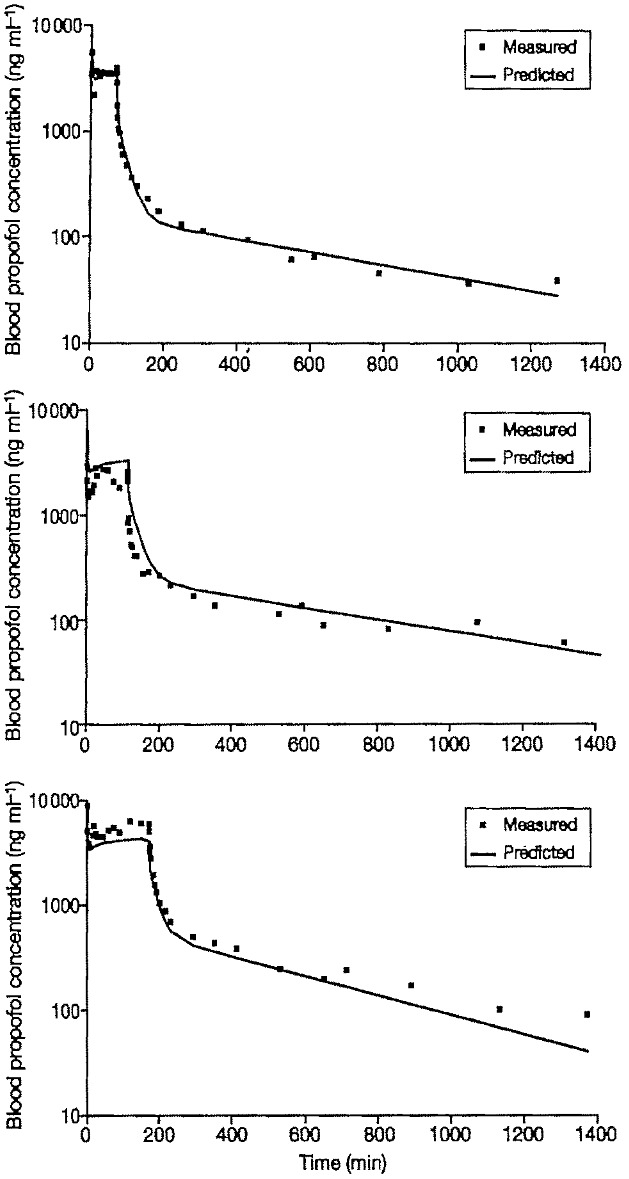

Fig 1 Measured and predicted propofol concentrations based on the complex pharmacokinetic model in the patient with the best predicted propofol concentrations (upper panel; MDPE (interquartile range) 0% (-11 to 10%) and MDAPE 11% (5–26%)) and in two patients with the most overpredicted (middle panel: MDPE -26% (-45 to -5%) and MDAP 32% (14–47%) and underpredicted propofol concentrations (lower panel: MDPE 32% (1–47%) and MDAPE 32% (12–49%)).

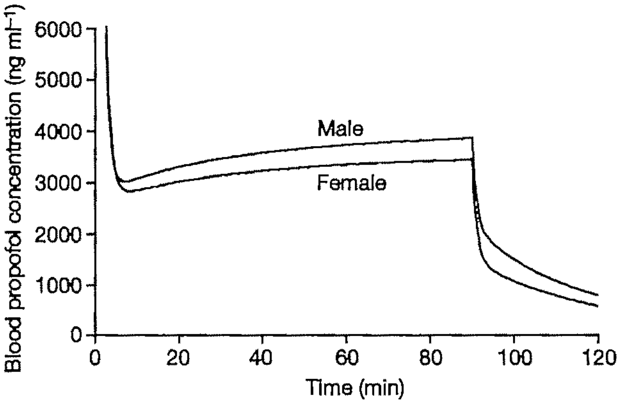

Fig 2 Predicted concentration-time relationship in an elderly female and male patient (both aged 73 yr, weighing 75 kg and being 180 cm tall) who receive a propofol bolus dose of 1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} for 89 min. Based on the complex pharmacokinetic model of this study, the predicted propofol concentrations during continuous infusion of propofol are 10–15% higher in male compared to female patients receiving the same infusion scheme.

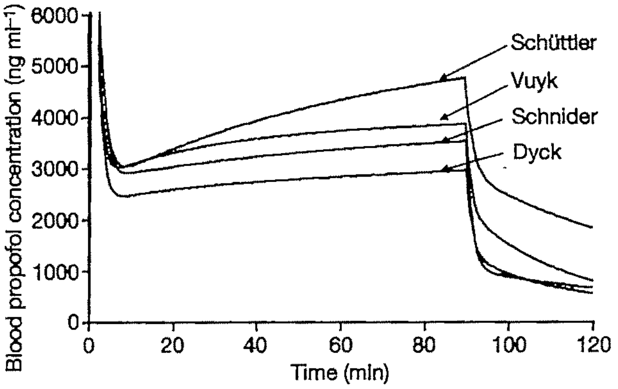

Fig 3 Predicted concentration-time relationship in an elderly male patient (aged 73 yr, weighing 75 kg and being 180 cm tall) who receives a propofol bolus dose of 1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} for 89 min as based on the pharmacokinetic parameter sets determined by Dyck and Shafer,[1] Schnider and colleagues,[2] Schüttler and colleagues[3] and in this study. Compared with the prédicted propofol concentrations based on the pharmacokinetic model of this study, the pharmacokinetics by Schüttler and colleagues[3] result in concentrations that are 20% higher, in contrast to those based on the pharmacokinetic parameter sets by Schnider and colleagues[2] and Dyck and Shafer[1] that result in concentrations that are 5 and 15% lower.

Gender differences in relation to other i.v. anaesthetics

The female patients in this study exhibited a larger slow peripheral volume of distribution (V_3), a higher metabolic (Cl_1) but reduced rapid peripheral clearance (Cl_2) compared with male patients. With respect to other i.v. hypnotic agents, the gender related changes in the pharmacokinetics of propofol closely correspond to those of midazolam described by Greenblatt.[8] The clearance of midazolam is lower and the volume of distribution is larger in female compared with male patients. In contrast, with thiopental, gender has no effect on the pharmacokinetics.[9] Similarly, for the opioids remifentanil and sufentanil the pharmacokinetics are unchanged between male and female patients.[10 11] Of the opioids, only alfentanil exhibited a gender effect on the pharmacokinetics; the central compartment was 15% larger in female compared with male patients in a study by Maitre and colleagues.[12]

Computer simulation of propofol pharmacokinetics in the elderly

The clinical consequences of the pharmacokinetics of propofol observed in this study were compared with those

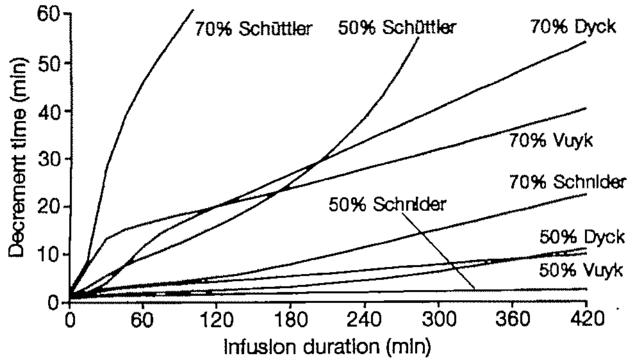

Fig 4 Fifty per cent and 70% decrement times (DT) *vs* infusion duration, based on the pharmacokinetic parameter sets determined by Dyck and Shafer,[1] Schnider and colleagues,[2] Schüttler and Ihmsen[3] and in this study. Fifty per cent and 70% decrement times are defined as the times required for the propofol concentration to drop by 50 or 70% after termination of a target controlled infusion that had been given with a constant target concentration for a given infusion duration.

based on the three parameter sets thus far described in the elderly[1-3] using a computer simulation of an infusion scheme as used in this study (1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} thereafter, Fig. 3). The measures of performance of these three other parameter sets in relation to those determined in this study were determined (Table 2). The computer simulations reveal that, based on the pharmacokinetics described in this manuscript, the predicted blood propofol concentrations are somewhat higher than those based on the pharmacokinetic data reported by Dyck and Shafer[1] and Schnider and colleages.[2] This may be the result of the fact that in contrast to the patients of Dyck and Shafer[1] and Schnider and colleages,[2] our patients were studied in a clinical setting and received alfentanil in addition to propofol. Recently, alfentanil has been shown to affect the pharmacokinetics of propofol such that in the presence of alfentanil propofol concentrations are increased by about 18%.[5] In that study, alfentanil reduced both the volume of distribution and the clearance of propofol. The mechanism of this interaction remains yet unknown.

In contrast to the data reported by Dyck and Shafer[1] and Schnider and colleagues,[2] the recently described population pharmacokinetic parameter set by Schüttler and Ihmsen[3] correlates much less with our data (Table 2, Fig. 3). Schüttler and Ihmsen[3] evaluated propofol concentration-time data from a heterogeneous data set. Compared with the previously described data sets[1 2] and the data reported in this study, the central compartment is larger and the clearance much smaller in the data set described by Schüttler and Ihmsen.[3] Consequently, 50 and 70% decrement times in the elderly calculated from the data of Schüttler and Ihmsen are very different from those calculated from the other studies (Fig. 4). Compared with our data and those by Dyck and Shafer[1] and Schnider and colleagues[2] the predicted propofol concentrations during propofol infusion based on the data of Schüttler are significantly higher (Fig. 3). Whereas according to our pharmacokinetic parameter set and those of Dyck and Shafer[1] and Schnider and Ihmsen[2] the propofol concentration during constant-rate infusion remains stable after approximately 90 min of infusion. The propofol concentrations continue to increase according to the pharmacokinetic parameter set by Schüttler and Ihmsen[3] resulting in 60–70% higher predicted concentrations after a 6 h infusion. What may be the cause of this discrepancy? Of the 270 patients studied by Schüttler and colleagues[3] only a small minority was aged 65 yr or older (approximately 10%) in contrast to for instance a large group of patients aged 11 yr or younger (approximately 35%). Furthermore, from the three groups of patients that contained elderly patients (groups 3, 5 and 7) the patients from group 5 only received a bolus dose of propofol. Clearly, evaluation of the concentration–time data from these patients will be less useful for application in a continuous infusion setting such as TCI. From the remaining elderly patients (groups 3 and 7) concentration–time data were only gathered for a mean period of 55 min. From these data taken over such a short period, it is difficult, if not impossible, to accurately estimate the metabolic clearance and/or slow distribution clearance of propofol. Methodological issues, thus, have led to a population pharmacokinetic parameter set that, in elderly patients, is considerably different from the pharmacokinetic parameter set presented in this manuscript and those described by Dyck and Shafer[1] and Schnider and colleagues.[2] Consequently, when applied in TCI the Schüttler pharmacokinetic parameter set will result in propofol concentrations that will be significantly lower than the desired target concentration and will decrease with increasing infusion duration.

The use of the Diprifusor® in the elderly

Many anaesthetists use the Diprifusor® (Zeneca Pharma, Macclesfield, UK) for target controlled infusion in elderly patients, although the pharmacokinetic parameter set incorporated has not included age or gender as covariates. We therefore evaluated the performance of the Marsh pharmacokinetic parameter set,[13] included in the Diprifusor®, in elderly patients. Figure 5 shows in the upper panel the infusion rates given to reach and maintain a target propofol concentration of 3 μg ml^{-1} by the Diprifusor® and by a TCI device provided with the pharmacokinetics determined in this study in an elderly male patient. As the Diprifusor® does not correct for the smaller V_1 and reduced clearance in the elderly,[2] during TCI the Diprifusor® will administer an unnecessary high infusion rate to maintain any desired target concentration in the elderly. The lower panel of this figure shows the estimated blood propofol concentrations using the pharmacokinetic parameter set determined in this study when provided with the infusion rate-time data required to reach and maintain a target propofol concentration of 3 μg ml^{-1} on the basis of the pharmacokinetic parameter set included in the Diprifusor®.[13] Figure 5 shows that using the Diprifusor® for TCI in the elderly will result

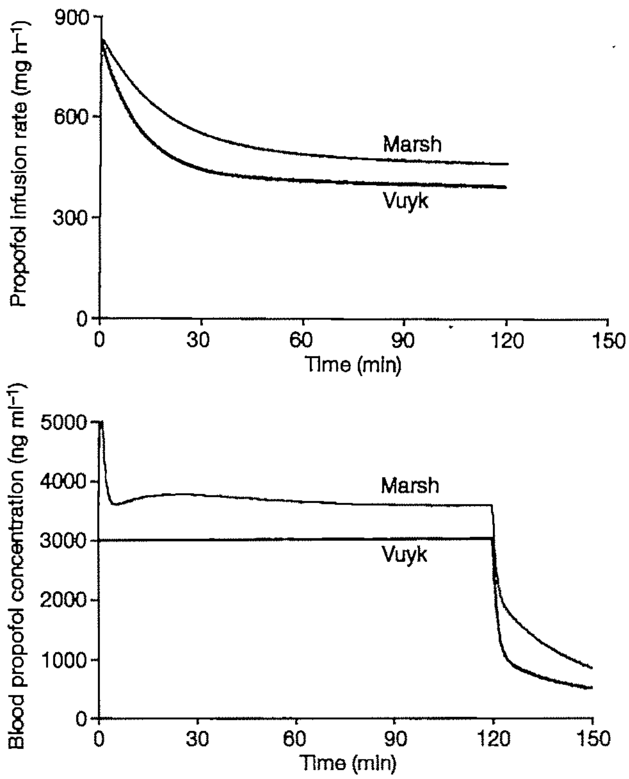

Fig 5 (Top panel) The infusion rates required to reach and maintain a target propofol concentration of 3 μg ml^{-1} for 120 min in an elderly male patient (aged 73 yr weighing 75 kg and 180 cm tall) as based on the pharmacokinetic parameter sets of this study and those used in the Diprifusor® by Marsh and colleagues.[13] (Bottom panel) The blood propofol concentrations as predicted by computer simulation using the pharmacokinetic parameter set of this study in an elderly male patient (aged 73 yr, weighing 75 kg and 180 cm tall) when provided with the infusion rate-time data required to reach and maintain a target propofol concentration of 3 μg ml^{-1} on the basis of pharmacokinetics incorporated in the Diprifusor® by Marsh and colleagues.[13]

in blood propofol concentrations that are approximately 20–30% higher than the targeted. Again based on our data this discrepancy will be 10% smaller in female compared to male patients. Consequently, on pharmacokinetic grounds the target concentration in elderly patients should be reduced equivalently to assure a similar effect as in younger patients. Age related pharmacodynamic changes[14] will require an even further reduction in target concentration with increasing age to assure a stable effect of propofol in patients of all ages.

We defined the pharmacokinetics of propofol when given by continuous infusion in female and male patients aged 65–91 yr in a clinical setting in the presence of alfentanil. Gender affects the pharmacokinetics of propofol in elderly patients resulting in lower concentrations in elderly female patients compared to elderly male patients given the same infusion scheme. Consequently, elderly female patients should be given approximately 10% higher infusion rates compared with elderly male patients to assure the same blood propofol concentration is reached.

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Comparing the effects of stimulation and propofol infusion rate on implicit and explicit memory formation

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Doubt remains about the conditions under which learning persists despite anaesthesia. This study investigated the relative importance of dose of anaesthetic and stimulation for learning during propofol infusion before surgery. Thirty-six patients were randomly assigned to three groups. Group 1 received two word lists (category examples and nonsense words) during infusion of propofol to a target concentration of 2 μg ml^{-1}. Groups 2 and 3 received the word lists during infusion of propofol 5 μg ml^{-1}. Group 2 received nonsense words before tracheal intubation and category examples during intubation; Group 3 heard category examples before and nonsense words during intubation. Bispectral index was recorded as a measure of depth of sedation/anaesthesia. We assessed explicit memory on recovery using a structured interview and a recognition test. We assessed implicit memory using a category generation test and a preference rating task. To establish baseline, a control group of 12 patients completed the category generation test without receiving the category examples during anaesthesia. Overall, there was no evidence for learning during propofol infusion, though the category generation task showed a trend towards more implicit memory for words presented during intubation than during anaesthesia. We conclude that learning does not occur during anaesthesia without surgery.

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Many studies have demonstrated learning during general anaesthesia.[1 2] In a typical study, patients are played a tape of words during surgery and then given memory tests for these words on recovery. The memory tests reveal unconscious or implicit memory for the words even though patients have no conscious or explicit memory of hearing anything during their operation. That is, patients respond differently on the implicit memory tests to the words that were presented during anaesthesia compared with similar distractor words, yet they neither recall hearing the words during anaesthesia nor recognize these words when they are presented on recovery. It is not known whether this learning occurs despite patients being unconscious or whether it is a sign that some patients are momentarily conscious during anaesthesia. The effects of surgery and other types of stimulation on learning are also unknown. Volunteer studies have tended to show little or no learning during conscious sedation, unless the dose of anaesthetic is very small and the stimuli to be learned are simple, such as single words.[3] Volunteers differ from patients in two ways: absence of surgical stimulation and, presumably, lower levels of anxiety. Surgery and anxiety may facilitate learning by decreasing the depth of anaesthesia or by altering concentrations of circulating catecholamines independently from their effects on anaesthetic depth.

This study investigated the relative importance of dose of anaesthetic and stimulation for learning during propofol infusion. We tested patients immediately before their scheduled operations, assuming that they would be more anxious and therefore more likely to learn than volunteers who, in a previous study, had shown no memory for words presented during propofol sedation.[3] We manipulated the depth of anaesthesia experimentally by presenting words to one group of patients receiving a small, sedative dose of propofol and to another group receiving a light anaesthetic dose of propofol. We used the bispectral index[4] to check that these depth manipulations were effective. We assessed the effect of physical stimulation by comparing memory for words played during anaesthesia without stimulation with memory for words played during tracheal intubation with

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the same dose of anaesthetic. Memory for the words was assessed on recovery using recognition tests plus a category generation test and a preference rating task. These latter tests have been shown to reveal memory even in the absence of conscious recognition.[5 6] Category generation was used for comparison with previous demonstrations of learning during general anaesthesia.[7 8] Preference ratings have also been used to demonstrate learning during sedation[9] and anaesthesia,[10] but were chosen specifically because they are sensitive to emotional changes caused by levels of learning that are insufficient to produce the cognitive changes that are picked up by more conventional tests of implicit memory.[11 12]

Methods

Memory tests

Implicit memory was tested by a category generation task and by a preference rating task. Full details of the construction and pilot-testing of the memory tests are given in the Appendix.

The stimuli for the category generation task were 30 repetitions of the words 'yellow banana green pear', which have been used in previous demonstrations of learning during anaesthesia.[7 8] These stimuli were played during the propofol infusion. In the test (on recovery), patients were asked to say the first three fruits and first three colours that came to mind. Implicit memory is revealed in this task as an increased tendency to respond with the previously presented examples of fruits and colours.

The stimuli for the preference rating task were 12 repetitions of 10 nonsense (Finnish) words. One list of 10 Finnish words was presented before propofol infusion and a second list, containing a different set of 10 Finnish words, was presented during propofol infusion. Implicit memory increases liking or preference, a phenomenon known as the 'mere exposure effect';[12] patients were therefore asked to rate their liking or preference for presented and distractor Finnish words. Pilot-testing with a sample of undergraduates validated the preference rating test as a test of implicit memory and provided an estimate of effect size for the test. Explicit, or conscious, memory was tested by asking patients a standardized set of questions about their recall of peri-operative events, and by asking them to rate their recognition of the Finnish words.

The different memory tests necessitated different control procedures. For the preference rating test, baseline measures were provided by asking patients to rate distractor words and presented words, the use of word lists as 'distractor' or 'presented' being fully counterbalanced across patients. For the category generation task, a baseline measure was provided by asking a control group of patients to generate examples of fruits and colours without prior exposure to the stimulus words.

Pre-operative procedure

Approval was granted from the North Sheffield Local Research Ethics Committee. We obtained written informed consent from 37 females, ASA status I and II, attending the Northern General Hospital for laparoscopy. Exclusion criteria were perceptible hearing loss, language difficulties, neurological dysfunction, treatment with drugs affecting the central nervous system, and the ability to speak or understand Finnish.

Patients were unpremedicated and entered the anaesthetic room approximately 25 min before the scheduled start of their operation. Bispectral index (BIS) monitoring was commenced with an Aspect-1000 monitor (software version 2.51; Aspect Medical Systems, Framingham, MA, USA) with bifrontal montage (F7, F8, reference Fp2). BIS was monitored continually throughout the study period. Patients were asked to lie comfortably and the experimenter explained that a list of Finnish words would shortly be played and that they should try hard to remember as many words as possible. They were reassured that they were not expected to understand the words and that they should concentrate on the sounds of the words. They were told that their memory for the words, and for some more words presented during anaesthesia, would be assessed when they came round from the anaesthetic. The first list of Finnish words was played via headphones (Sony MDR-CD170) using a portable compact disk player (Sanyo MCD-Z37L). This pre-operative list of words served to make the post-operative memory tests more meaningful to patients by ensuring that they remembered at least some of the stimulus words. The experimenters (LE and CH) were blinded to the content of the Finnish tracks.

An i.v. cannula was then inserted for the infusion of propofol and a second i.v. cannula was inserted into the contralateral arm for the collection of blood samples.

Patients were randomized to one of three groups. In one patient, memory testing could not be carried out and she was replaced. The preference rating task was designed to be more sensitive than tests used previously in studies of learning during anaesthesia. As it had not been used before with patients, we conducted a pilot study (described in the Appendix) to estimate its power to detect memory under conditions of altered awareness. Pilot data gave an effect size of 0.74 for the preference rating memory test under conditions of divided attention; we therefore estimated power for detecting implicit memory as 0.99 for the whole patient sample and 0.73 for single groups.

Group 1

Patients in group 1 received a sedating dose of propofol by computer-controlled infusion using a Graseby Diprifuser pump to a target concentration of 2 $\mu g\ ml^{-1}$. After 10 min, a blood sample was taken for determination of plasma propofol concentration. The experimenter then instructed patients to listen carefully and try to remember the Finnish words, and then played the second list of Finnish words.

After a break of approximately 1 min, the experimenter repeated the instruction to listen carefully and remember the words, then played the list of category examples. After this, the target propofol infusion was increased to 5 μg ml^{-1} to achieve full anaesthesia. Patients then received vecuronium 5 mg, their tracheas were intubated and the patients were transferred to the operating theatre for surgery. All patients then received fentanyl 1 μg`ml^{-1} i.v. and anaesthesia was continued with propofol to a target concentration of 5 μg ml^{-1} and artificial ventilation with 60% nitrous oxide and 40% oxygen. At the end of surgery, residual neuromuscular block was reversed with neostigmine and glycopyrollate. Propofol was turned off and patients were woken as normal before being taken to the recovery ward.

Groups 2 and 3

Patients in groups 2 and 3 received a higher initial dose of propofol to a target concentration of 5 μg ml^{-1}. After 10 min, a blood sample was taken for propofol assay. Patients in group 2 received the second list of Finnish words and patients in group 3 received the list of category examples. All patients then received vecuronium 5 mg and had their tracheas intubated. From the start of laryngoscopy, patients in group 2 received the category examples and patients in group 3 received the Finnish words. Anaesthesia then continued as for group 1. Only one list was presented during intubation because we suspected that the stimulation caused by intubation would not last for the time taken to present two lists.

Plasma analysis

Blood taken for propofol assay was stored at 4°C in oxalate and the assay was performed by high-performance liquid chromatography with fluorescence detection.[13]

Post-operative procedure

Patients attempted the memory tests in the recovery room as soon as possible after surgery (within 2 h of recovery). Post-operative analgesia was provided with i.v. boluses of morphine 2 mg as required. Before the patients attempted the tests, we ensured that they were comfortable and felt able to sit up in bed and perform them. Memory was tested as follows. First, all patients were asked to name the first three examples of vegetables (for practice), fruits and colours that came to mind. Then they were asked if they could remember anything about their operation or about events occurring immediately before their operation. They were also asked whether they remembered dreaming during this period. Questioning became progressively more specific: patients were asked whether they remembered listening to any words before or during their operation, hearing the names of any vegetables, fruits or colours, hearing any Finnish or other foreign words, and finally whether they recognized any of the exemplars they had just generated or examples from the phrase 'yellow banana green pear'. Responses were written down by the experimenter.

The Finnish memory tests came next. For the implicit memory test, patients were asked to decide whether each word referred to something good or nice, or to something bad or nasty. As they did not understand Finnish, they were asked to guess, using the strategy of assuming that a word refers to something nice if it sounds nice and to something unpleasant if it sounds unpleasant. These instructions deliberately implied that there was a correct answer, even though patients were being asked to guess, to encourage diversity of responses.[11] For the recognition task, patients were asked to decide which words they remembered hearing earlier in the procedure, regardless of whether they came before or during the propofol infusion. Patients wrote down their own responses for this phase of testing. Patients heard the test list twice, rating their preference or recognition of each word on a 4-point scale. Test order was counterbalanced, i.e. half the patients in each group rated recognition on the first presentation of the test list and rated preference on the second presentation; the other half rated preference first and then recognition. On the second presentation, patients were asked to ignore the fact that they had just heard the entire list once. Ideally, we would have tested preference for half the words and recognition for the other half, but this would have required more stimuli and it is not known how initial memory load affects subsequent explicit and implicit memory under these conditions.

Control group for the category generation test

A control group of a further 12 patients was needed for the category generation test of implicit memory. This group was selected from patients undergoing laparoscopy on the same surgical lists as those in the experimental groups, and fulfilling the same criteria, but whose scheduled operation time meant that they could not be anaesthetized for the extended period required by the experimental conditions.

Statistical methods

BIS readings were recorded at the start and end of each memory list, and a mean was calculated for each list for each patient. Two-way mixed measures analysis of variance was used to compare the mean BIS values for each list across the three groups, followed by planned t-tests. One-way independent measures analysis of variance was used to compare propofol blood concentrations across groups, again followed by planned t-tests.

Category generation test performance was scored as the number of 'hits' (responses with one of the words 'yellow', 'banana', 'green' or 'pear'). The independent samples t-test was used to compare mean hits in the experimental groups with mean hits in the control group, and to compare across experimental groups. The preference rating and recognition tasks were scored from 3 for a response of 'definitely remember' or 'very nice' response to 0 for a response of 'definitely do not remember' or 'very nasty' response. Dependent samples t-tests were used to compare scores for presented words with those for distractor words, and to compare intraoperative learning, if found, across groups. To maximize the chance of detecting memory, we did not correct the t-test results to allow for multiple testing. Statistical significance was assessed with $\alpha = 0.05$ and all tests were two-tailed. All analyses were performed using StatView 5.0.

Results

One patient in group 3 received additional propofol (50 mg bolus) because she moved just before intubation. Fifteen patients received morphine in the recovery area before memory testing (dose range 2–10 mg). Five of these patients were in group 1, four were in group 2 and six were in group 3.

BIS was significantly reduced in all three experimental groups after starting the propofol infusion ($P<0.01$) (Table 1). BIS was significantly lower in the two groups receiving propofol 5 μg ml^{-1} infusion than in the group receiving 2 μg ml^{-1} infusion ($P<0.001$). In all patients, we noted an increase in heart rate after intubation. However, BIS scores were not significantly altered by intubation. Blood propofol concentrations were significantly higher in groups 2 and 3 than in group 1.

Explicit memory

No patient reported recall of surgery. One patient in group 1 recalled hearing the category examples ‘banana’, ‘pear’ (both presented during infusion of propofol 2 μg ml^{-1}) and ‘orange’ (not presented). One patient in group 2 recognized ‘banana’ (presented during intubation) when read the phrase ‘yellow banana green pear’. All but two patients remembered hearing nonsense or Finnish words some time before their operation. One patient claimed to remember the entire period of sedation with propofol 2 μg ml^{-1} but could not recall any of the Finnish words. Four patients reported hearing a total of 13 Finnish words, six of which came from the list played before propofol infusion and seven of which were unidentifiable. No-one recalled Finnish words from lists played during propofol infusion.

Recognition scores for the Finnish words showed explicit memory for the list presented before propofol infusion began ($P<0.001$), but no memory for the list presented during propofol infusion (Table 2).

Implicit memory

Category generation hits for the experimental groups did not differ significantly from those for the control group, nor were there more hits when the phrase was presented during sedation than when it was presented during anaesthesia (Table 3). There was a tendency ($P=0.06$) for more hits when the phrase was presented during intubation compared with during anaesthesia before intubation.

Preference ratings for the Finnish words showed implicit memory for the words presented before propofol infusion began ($P<0.05$). For the words presented during propofol infusion, ratings did not differ from baseline, i.e. there was no implicit memory.

To maximize power, we tested implicit and explicit memory for the whole set of Finnish words. However, the second presentation of the test list was possibly a less sensitive memory test than the first, because patients had to distinguish words they had heard earlier from the whole set

Table 1 Bispectral index during stimulus presentation and mean blood propofol concentration just before presentation of list 2. Mean (range). Within-group comparisons: *$P<0.01$ compared with list 2 BIS values. Between-group comparisons: **$P<0.001$ compared with groups 2 and 3

Group	Bispectral index			Blood propofol concentration (μg ml^{-1})
	List 1: before propofol infusion	List 2: during sedation (group 1) or anaesthesia (groups 2, 3)	List 3: during sedation (group 1) or intubation (groups 2, 3)	
1	92.0 (88.5–95.5)*	85.4 (76.5–96.5)**	82.4 (65.0–96.0)	0.89 (0.19–2.36)**
2	91.2 (82.5–96.5)*	51.3 (29.5–73.0)	51.9 (33.0–71.5)	2.77 (0.73–5.40)
3	90.5 (76.0–95.5)*	55.8 (45.5–70.0)	54.8 (44.5–62.0)	3.13 (0.63–5.50)

Table 2 Mean explicit and implicit memory scores for the Finnish words, by anaesthetic condition during word presentation. Mean (95% confidence interval). Memory scores are presented as priming index, i.e. score for presented list minus score for distractor list. *$P<0.05$; **$P<0.001$, one-tailed t-test comparing priming index with zero

Condition	Explicit memory (recognition)	Implicit memory (preference ratings)
Before propofol (all groups)	9.41 (7.16 to 11.65)**	1.63 (0.12 to 3.13)*
Sedation (group 1)	–0.08 (–2.96 to 2.79)	–0.13 (–3.32 to 3.07)
Anaesthesia (group 2)	1.52 (–2.37 to 5.42)	–1.08 (–2.99 to 0.82)
Anaesthesia + intubation (group 3)	1.36 (–1.42 to 4.14)	–0.50 (–2.46 to 1.46)
Mean priming score for words presented during propofol infusion (all groups)	0.93 (–0.75 to 2.62)	–0.57 (–1.83 to –0.69)

Table 3 Number of hits on the category generation test, for patients who received the phrase 'yellow banana green pear' during propofol infusion and the control group, who did not receive the phrase. *P=0.06 compared with anaesthesia (group 3). No other comparisons were significant (P>0.10)

Phrase during which phrase was presented	Mean number of hits
Sedation (group 1)	1.83
Anaesthesia (group 3)	1.67
Anaesthesia + intubation (group 2)	2.08*
Mean for the experimental groups	1.86
Mean for the control group	1.75

of words that they had just heard. We therefore analysed the responses of each group to the first presentation of the test list, i.e. the preference rating task for half the patients and the recognition task for the other half in each group. Groups 1 and 2 showed no difference between ratings for the words presented during propofol and distractors. Group 3 had marginally higher ratings for the words presented during intubation with propofol infusion than the distractors (P=0.09).

Discussion

We experimentally manipulated depth of anaesthesia in two ways, by varying the propofol infusion rate and by giving the stimulus of tracheal intubation. To confirm this, we used BIS as an index of depth of sedation/anaesthesia. Our results confirmed that depth of anaesthesia differed between patients receiving propofol 2 $\mu g\ ml^{-1}$ and those receiving 5 $\mu g\ ml^{-1}$. However, BIS did not detect an effect of intubation in the patients receiving propofol 5 $\mu g\ ml^{-1}$ (Table 1). Intubation is known to be a stimulating procedure, and there were clinical signs of lightened anaesthesia (increased heart rate) when patients were intubated in the present study. The failure of BIS to detect any effect of intubation may reflect its insensitivity to subtle changes in anaesthetic depth or suggest that BIS is a better monitor of depth of sedation than depth of anaesthesia.

We tested implicit and explicit memory for category examples and Finnish words presented during propofol infusion. Overall, there was no evidence of explicit or implicit memory for category examples presented during propofol infusion. There was a suggestion of implicit memory for the examples presented during intubation compared with anaesthesia without intubation, but this result must be treated with caution because (i) it was only marginally significant and would have been non-significant after correcting for multiple t-testing; (ii) the hit rate in the intubation condition was not significantly higher than for the control group. We observed explicit and implicit memory for the Finnish words presented before propofol infusion, despite the intervening anaesthesia and surgery. Overall, there was no memory for the Finnish words presented during propofol infusion, but again there was a weak trend towards memory for words presented during intubation. Further investigation of the effects of stimulation on learning may be worthwhile.

We obtained absolutely no evidence for learning during propofol infusion without stimulation. This study incorporated methodological improvements upon many previous studies. We used a single anaesthetic agent during stimulus presentation and tested patients scheduled for the same operation, thereby minimizing noise compared with opportunistic studies that tested patients receiving various drugs. Recall tests tend to be more difficult than recognition tests or implicit memory tests because they provide no information about the words to be remembered. We tried to make the explicit and implicit memory tests equally sensitive by using recognition for the explicit tests;[14] therefore failure to observe explicit memory shows a genuine lack of explicit, conscious learning and not merely failure on a difficult test. We piloted the Finnish memory tests to confirm that the recognition test measured explicit memory and the preference rating test measured implicit memory. We manipulated depth of anaesthesia experimentally and measured it using the bispectral index.

A previous study has shown implicit memory for words presented to volunteers receiving propofol,[15] but the infusion dose of propofol was considerably smaller (1.27 $mg\ kg^{-1}\ h^{-1}$) than the 2 $\mu g\ ml^{-1}$ used in the present study. Volunteers failed to learn words presented during infusion of larger subanaesthetic doses of propofol.[3 16] In contrast, studies with patients showed learning during surgery with sedative infusions of propofol,[17 18] and general anaesthetic regimes that included propofol[7 18–22] (though some have shown no learning).[23–25]

Volunteers may learn relatively little because they are not anxious and do not attend carefully to the stimuli while they are sedated (although lack of attention should have little effect on implicit memory). We assumed that the patients in our study would be more anxious and more attentive, yet they learned nothing even during conscious sedation. The evidence from other studies that patients can learn during surgery with propofol sedation or anaesthesia suggests that surgery may enable learning in anaesthetic conditions that would otherwise prevent learning. The present finding that patients showed marginally significant amounts of memory for words presented during intubation yet no memory for words presented during sedation, tentatively supports the hypothesis that physical stimulation facilitates learning. A stronger relationship may have been found if the period of stimulation had been longer. A recent study of learning during trauma surgery[26] demonstrated that depth of anaesthesia (BIS) explained a modest portion of the variance in memory for intraoperative stimuli. We speculate that levels of physical stimulation would explain another portion of the memory variance, perhaps through increases in concentrations of circulating catecholamines.

Any conclusions must be considered in the light of the several weaknesses in the study. To avoid undue disruption to operating theatre schedules, we did not subject the control group for the category generation task to the full preoperative sedation protocol. Rather, we selected patients for the control group whose scheduled operation time made them unsuitable for the full procedure. Although a fully randomized group would have been preferable, we are reassured by the fact that our control group's response rate (1.75) was similar to that reported by Jelicic and colleagues[8] (1.84), though both differed from the baseline rate in a previous study[7] of patients undergoing major surgery (0.79). Time constraints prevented us from testing anxiety levels but future research could investigate the effect of preoperative anxiety on learning during anaesthesia. Fifteen patients received morphine before attempting the memory tests. Morphine may have affected their performance on the tests, as might the pain they would have experienced without morphine. Either way, it would have been unethical to withhold analgesia. We presented the full test list of Finnish words twice, once for the preference test and once for the recognition test. Ideally, we would have tested preference for half the words and recognition for the other half, but this would have required more stimuli and it is not known how initial memory load affects subsequent explicit and implicit memory under these conditions. Despite these weaknesses, we conclude that sedation and anaesthesia with propofol prevents learning. We observed a trend towards memory for stimuli presented during the brief stimulation caused by tracheal intubation. We therefore speculate that more prolonged stimulation may facilitate learning during anaesthesia.

Appendix

Construction of the memory stimuli and tests

Category generation task

Thirty repetitions of the phrase 'yellow banana green pear' were recorded onto a compact disc track at the rate of one word per 1.5 s, making a total presentation time of 3 min.[7,8] The phrase was played to the patients during propofol infusion, and on recovery they were asked to say the first three examples of fruits and colours that came to mind.

Preference rating and recognition tasks

Three lists of ten disyllabic Finnish words were recorded onto compact disk, one list per track. Each list was repeated 12 times at the rate of one word per 1.5 s hence a total list length of 3 min. A single test list, containing all 30 words in random order, was recorded onto a separate compact disk track with a 4 s interval between each word and the next. The response sheet for the preference rating task contained five columns, one listing the 30 words and the other four headed 'very nice/good', 'slightly nice/good', 'slightly nasty/bad' and 'very nasty/bad'. On the response sheet for the recognition task, columns 2–5 were headed 'definitely remember', 'seems familiar', 'seems unfamiliar' and 'definitely do not remember'. A score of 3 points was given for each 'definitely remember' or 'very nice' response, two points for each 'seems familiar' or 'slightly nice' response, 1 point for each 'seems unfamiliar' or 'slightly nasty' response, and 0 points for 'definitely do not remember' or 'very nasty' responses.

Patients received one list of Finnish words before propofol infusion and a second list during propofol infusion. The third list provided distractors for the memory tests; the use of lists before propofol, during propofol or distractor was fully counterbalanced. On recovery, patients rated their preference and recognition of all 30 words.

Pilot testing

The Finnish stimuli and tests were pilot-tested on 12 undergraduate volunteers who listened to one list (repeated 12 times) with instructions to attend fully and remember the sounds of the words, and to a second list (repeated 12 times) under conditions of divided attention, the second list being presented as background distraction to a demanding visual task. After a 10 min filled retention interval, volunteers listened to the test list and rated their preference for each word. They then listened again to the test list and rated their recognition of the words. Two-factor analysis of variance with repeated measures on test (preference, recognition) and condition (focused attention, divided attention) showed a significant interaction between test and condition ($P<0.01$). Divided attention reduced recognition test scores compared with focused attention (paired t-test, $P<0.001$) but did not affect preference ratings ($P>0.10$). Ratings in each condition on each test exceeded the relevant baseline ratings to distractor words (paired t-test, $P<0.05$ for each comparison). These results show that the recognition test is a good measure of explicit memory, because it was sensitive to the manipulation of attention, and that the preference rating task is a good measure of implicit memory, because it was insensitive to the manipulation of attention yet showed higher ratings for presented words than distractors.

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Absence of memory for intra-operative information during surgery with total intravenous anaesthesia[†]

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While using the isolated forearm technique, we wished to determine whether patients who did not respond to commands during general anaesthesia with a total intravenous technique (propofol and alfentanil with atracurium) had any evidence of post-operative explicit or implicit memory. Forty women undergoing major gynaecological surgery were randomized, in a double-blind design, to hear two different tapes during surgery. Psychological tests of explicit and implicit memory were conducted within 2 h of surgery. There was no evidence of implicit or explicit memory, nor any recall, in the seven women who responded to commands during surgery. We conclude that during total intravenous anaesthesia with propofol and alfentanil, there is no evidence that learning takes place when anaesthesia is adequate. Furthermore, with this anaesthetic technique, it would seem that—provided any period of patient responsiveness is short and that unconsciousness is induced rapidly again—there is no evidence of implicit or explicit memory.

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Many publications suggest that patients can recall information presented to them during surgery; these studies are discussed in detail in several reviews.[1–4] However, while there is agreement that memory for new information exists after surgery, there is debate as to the level of consciousness of the patients when the intra-operative information was presented to them (i.e. were the patients adequately anaesthetized?). Merikle and Daneman[3] performed a meta-analysis of the literature and stated that there is 'considerable evidence that specific information is both perceived during anaesthesia and remembered following surgery'. However, the authors assume that 'patients who are undergoing general anaesthesia are ... unconscious of all external events for the entire duration of surgery'. The studies included in the meta-analysis provide no evidence that patients were in fact anaesthetized (i.e. unconscious and unresponsive) when information was presented. This is a problem with much research in this area. Andrade[2] states that during 'clinically adequate anaesthesia it is not yet clear that patients were actually unconscious when stimuli were presented'. At present the only direct method of detecting a responsive state during surgery is the isolated forearm technique (IFT). By using a tourniquet on one arm to prevent muscle relaxants paralysing the hand muscles, the IFT allows a patient to respond, should they become conscious during surgery, to verbal commands such as 'Open and close the fingers of your right hand.'[5–9] All electronic brain monitors assess consciousness indirectly and the IFT is the 'gold standard' against which all such monitors must be tested.[10 11] Use of the IFT has shown that some patients can respond to commands during surgery without any other outward sign of responsiveness.[5–9] If patients are given information during such an awake responsive state, it would not be surprising that sophisticated psychological tests detected evidence of memory for this information after surgery.

A previous study using the IFT with inhalational anaesthesia (nitrous oxide and halothane) found no evidence of post-operative recall for information presented to patients at

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[†] This study was initially presented at the Fourth International Symposium on Memory and Awareness in Anaesthesia, held at Northwick Park on July 10–12, 1998; an abbreviated form of the results was published in the book of abstracts from that meeting.

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a time when they were unresponsive to commands.[9] Investigations of total intravenous anaesthesia (TIVA) with etomidate[7] and midazolam[8] found 7% and 72% incidence of responsiveness, respectively, during surgery compared with zero incidence during inhalational anaesthesia.[9] It has been argued that awareness is a greater risk with TIVA than with inhalational anaesthesia.[12 13] With the growing popularity of propofol-based TIVA, we wished to study the incidence of intra-operative responsiveness of patients anaesthetized with this technique and also if patients could recall information presented during surgery at a time when the patient was known to be unresponsive to commands. Nordstrom and colleagues[14] described a simple TIVA regimen using only one infusion pump and, equally importantly, they also provided data on the incidence of post-operative recall (5/2500). With such a well documented incidence of recall, we decided to base our study on this regimen.

Methods

Approval for the study was obtained from the Hull and East Yorkshire ethics and clinical trials committee. The purpose of the trial was explained to women with no hearing difficulty presenting for major gynaecological surgery; their informed consent was obtained. After premedication with oral temazepam 20 mg, 1–2 h before surgery, the women were brought to the anaesthetic room. Intravenous access was obtained in the non-dominant arm with a 17 gauge cannula. An epidural catheter was then placed at L2/3 through an 18 gauge needle (lateral oblique approach, loss of resistance to 1 ml of 0.5% bupivacaine) and, after a negative aspiration test, a further 14–19 ml of 0.5% bupivacaine was injected incrementally over 5 min. The patient was then taken into the operating theatre, the various monitors were attached and, after a short period of baseline monitoring, general anaesthesia was induced.

The general anaesthetic was based on the propofol/alfentanil infusion regimen described by Nordstrom and colleagues.[14] Propofol and alfentanil were mixed in the same syringe as follows: propofol 500 mg plus alfentanil 2500 μg to a total volume of 55 ml, giving final propofol and alfentanil concentrations of 9.1 mg ml^{-1} and 45.5 μg ml^{-1}, respectively. Induction and anaesthesia were based on the propofol delivery from this mixture, with alfentanil in proportion. Induction was with propofol 2–2.5 mg kg^{-1}, infused at a rate of 600 ml h^{-1} and maintenance was a 10, 8, 6, 4 mg kg^{-1} h^{-1} stepdown (at 10 min intervals) infusion regimen. The propofol/alfentanil infusion was controlled by a Graseby 3400 infusion pump (Graseby Medical Ltd, Watford, UK) and a multilumen extension tube with non-reflux valves (Vygon Octopus; Vygon, Ecouen, France) was included between the infusion lines and the intravenous cannula to prevent backflow. Suxamethonium 1–1.5 mg kg^{-1} was administered and endotracheal intubation was performed. When the action of suxamethonium began to wear off, atracurium 0.2–0.4 mg kg^{-1} was used for more prolonged neuromuscular block. The lungs were ventilated with an air–oxygen mixture containing 35–40% oxygen through an Oxford Penlon mark II ventilator in its non-rebreathing configuration and end-tidal carbon dioxide was maintained between 4 and 5%.

For each patient, two identical looking 1 min continuous-loop cassette tapes (coded 'FG' for fruit group or 'VG' for vegetable group on the underside) were prepared by I.R. One to two minutes after skin incision, one of these tapes was played to the patients in a randomized double-blind manner. Randomization was achieved by means of codes contained in consecutively numbered brown envelopes. A colleague who was not involved in the trial had previously written the codes on to cards (20 cards for each code) and placed the cards individually into the envelopes. The envelopes were then mixed and numbered consecutively 1–40. During the trial the anaesthetic assistant opened the envelopes, wrote the envelope number and the name of the patient on each card and kept the cards in a large brown envelope until the trial was completed. The appropriate tape was chosen by the assistant, according to the code on the card, and placed in a tape recorder (Sony Professional Walkman). The remaining tape was kept hidden until the end of surgery when both tapes were then placed back in their identical plastic cases by the assistant. The tapes were personalized for each patient by inclusion of her preferred name before the command and the information. Each tape contained the same initial message which included the patient's preferred name: *[Name]*, *[Name]*, this is Dr Russell speaking. If you can hear me, open and close the fingers of your right hand, open and close the fingers of your right hand.' The second message differed between the tapes. One tape contained the information '*[Name]*, *[Name]*, this is Dr Russell speaking. Here are some special words I'd like you to remember: green pear, sharp lemon, sour gooseberry.' The second message on the other tape was '*[Name]*, *[Name]*, this is Dr Russell speaking. Here are some special words I'd like you to remember: frozen peas, butter beans, Chinese leaves.' To ensure that the patients heard no other extraneous information through the open dynamic headphones (Beyerdynamic DT 411), the 15 s intervals between the voice messages consisted of loud radio static.

If hand movements were observed during surgery, the tape was immediately switched off and the patient spoken to directly. The patients were reassured and then the hand responses to direct commands (e.g. 'Squeeze my fingers') and to conditional commands (e.g. 'If you are in pain, squeeze my fingers twice' followed by 'If you are comfortable, squeeze my fingers once') were assessed. Anaesthesia was then deepened with a bolus of the propofol/alfentanil mixture (equivalent to propofol 0.5 mg kg^{-1}) and the infusion rate was increased by the equivalent of propofol 1 mg kg^{-1} h^{-1} before the tape was switched on again. The infusion rate was then stepped down by 1 mg kg^{-1} h^{-1} at 10 min intervals.

At the end of surgery, the tape was switched off of at the same time as the propofol/alfentanil mixture, muscle relaxant was reversed as required with atropine/neostigmine (0.6 mg/1.2 mg) and the epidural was topped up with 10 ml of 0.125% bupivacaine containing diamorphine 3 mg.

Within 2 h of the end of surgery, the patients were questioned by I.R. for evidence of explicit or implicit memory. All patients were asked the same questions, without prompting, in the following order: (i) Do you remember coming into the anaesthetic room? (ii) Do you remember the epidural being inserted? (iii) Do you remember the sticky electrodes being placed? (iv) Do you remember going into the operating theatre? (v) What was the last thing you remember before going to sleep? (vi) What was the first thing you remember on waking up? (vii) Can you remember anything in between these two? (viii) Did you have any dreams? (ix) Tell me the first five fruits you can think of. (x) Tell me the first five vegetables you can think of. (xi) Now I want you to tell me the first word that comes into your head when I say a word to you: father, green, sharp, sour, frozen, butter, Chinese.

Isolated forearm technique

Padding was placed around the dominant forearm (usually right) and an isolating tourniquet cuff wrapped around this. The standard arterial pressure cuff for routine monitoring of arterial pressure was placed on the dominant upper arm and the arm was placed on an arm board where it could be clearly observed. To restrain the hand from sudden unexpected movements, a tie was placed lightly around the fingers and the arm board. A Datex Relaxograph was used to check neuromuscular transmission under and distal to the cuff. Stimulating electrodes were placed over the ulnar and median nerves at the elbow while the sensing electrodes were placed at the wrist and over the hypothenar eminence. As soon as consciousness was lost (as judged by absence of response to command), neuromuscular transmission was checked by observing the hand contractions as the Relaxograph went through its initial set-up procedure. When the paralysis after the intubating dose of succinylcholine began to wear off, the isolating cuff was inflated just before giving atracurium. The cuff remained inflated for 20 min before deflation. Whenever further atracurium was required, this same inflation/deflation process was followed. Neuromuscular transmission under and distal to the tourniquet was confirmed by observation of the hand and finger responses to the 'train of four' stimuli delivered every 20 s from the Relaxograph. Although the Relaxograph assesses the electrical activity of muscle groups, it was the observed hand responses that were of importance in ensuring that neuromuscular transmission was sufficient for the patient to respond.

Chi-squared tests and signal detection analysis[15] were used as appropriate.

Results

Forty women were recruited into the study. Their ages, weights and duration of tape exposure, together with an indication of the surgical procedures, are shown in Table 1. The difference in the mean duration of tape exposure in the two groups just failed to reach statistical significance (P=0.06). This difference was almost entirely due to one patient in the 'fruit' group undergoing very long surgery (lasting 280 min, 2.8 SDs above the mean).

No patient had explicit memory for any aspect of surgery or of the taped commands. Tables 2–6 indicate the results of tests of implicit memory from all 40 patients. These tables provide the 'hits' data and serial position scores for lists of both three and five exemplars. In the word association test (Table 6), there was only one 'hit', the word pair 'frozen peas'.

Table 1 Age, weight and tape duration for the two groups together with the type of surgery. †Mean (range). *Mean (SD)

	Group		*P* value
	'Vegetable'	'Fruit'	
Age (yr)	46.4 (35–45)†	40.3 (26–57)†	0.02
Weight (kg)	69.1 (15.7)*	66.1 (8.9)*	0.5
Tape duration (min)	78.9 (35.5)*	109.3 (58.8)*	0.06
Type of gynaecological surgery (n)			
Abdominal procedure	19	18	
Vaginal hysterectomy	1	2	

Table 2 Number of vegetable and fruit exemplar 'hits' when a list of five exemplars was requested; the total number of possible 'hits' is 60

Group	Vegetable 'hits' in list of five vegetables	Fruit 'hits' in list of five fruits
Vegetable (n=20)	8	14
Fruit (n=20)	7	14

Table 3 Number of vegetable and fruit exemplar 'hits' when a list of three exemplars was requested; the total number of possible hits is 60

Group	Vegetable 'hits' in list of three vegetables	Fruit 'hits' in list of three fruits
Vegetable (n=20)	5	6
Fruit (n=20)	7	5

Table 4 Serial position score based on list of five exemplars (score=5 for first position down to 1 for fifth position). Maximum score per patient= 12 (5+4+3). Maximum score per group=240

	Score	
Group	Vegetable	Fruit
Vegetable (n=20)	23	37
Fruit (n=20)	23	32

Table 5 Serial position score based on a list of three exemplars. Score=3 for first position down to 1 for third position. Maximum score per patient= 6 (3+2+1). Maximum score per group=120

	Score	
Group	**Vegetable**	**Fruit**
Vegetable (*n*=20)	10	10
Fruit (*n*=20)	10	9

Table 6 Word association 'hits'. Total possible hits per group was 60. *All seven of the word association 'hits' were 'frozen peas'

	Word association hits	
Group	**Vegetable**	**Fruit**
Vegetable (*n*=20)	4*	0
Fruit (*n*=20)	3*	0

Table 7 Group allocation and weight of patients who responded to commands, the times of the responses and the infusion rates at the time of the responses from seven patients with verified responses to commands. *At this time the patient indicated she was uncomfortable; the surgeon had just inserted a self-retaining retractor and was performing a thorough exploration of the upper abdominal cavity

Group of words/ patient	Weight (kg)	Time (min)	Propofol infusion rate (mg kg^{-1} h^{-1})
Vegetable group			
Patient a	55	34*	7
		64	5
Patient b	74	55	4
		80	5
Patient c	79	43	
Patient d	67	65	4
Patient e	83	55	4
		75	5
Fruit group			
Patient f	64	66	4
		105	5
		125	6
Patient g	66	60	4

Table 8 Number (proportion of total possible) of hits in those patients awake and responding during surgery compared with patients who did not respond during surgery. *This difference is not significant (P=0.48)

Category of patients (*n*)	Fruit or vegetable exemplars: correct hits	Word association hits
Responsive (7)	5 (24%)*	1 (6%)
Unresponsive (33)	17 (17%)*	6 (6%)

Seven women, two in the 'fruit' group and five in the 'vegetable' group, responded to commands at some stage during surgery. Among them, these women responded a total of 12 times at propofol infusion rates ranging from 4 to 7 mg kg^{-1} h^{-1} and at times ranging from 34 to 125 min into surgery (Table 7). On only one occasion did one of these women express her discomfort (Table 7). There was no evidence that these seven patients had a greater rate of recall than non-responding patients (Table 8).

None of the women had any side effects from the use of the isolating tourniquet.

Discussion

There is debate about whether familiar or unfamiliar words are more likely to be returned in memory tests,[2] so to cover both possibilities the exemplars presented to our patients spanned a wide range: from third through seventh to below fifteenth in their respective lists (the position of the exemplars in their respective lists had previously been established in our population of women presenting for major gynaecological surgery[16]). We asked each patient for five exemplars and analysed both three-exemplar and five-exemplar lists. This allowed a wider range of familiarity/ unfamiliarity to be assessed, increasing the chances of a positive effect. Despite this, we found no evidence of explicit or implicit memory for information presented during surgery under general anaesthesia. This result confirms previous published[8 9] and as yet unpublished studies[11] from this department but is contrary to many other results discussed in reviews.[1–4]

One possible reason for our negative findings could be that the memory tests we used were unsuitable. We do not believe this is a valid reason. In a literature review carried out in 1990,[16] seven studies were found which investigated word priming during general anaesthesia. Three of these studies obtained statistically significant evidence of word priming; in contrast to the four negative studies, these three positive studies used category association to cue recall of implicit memory. Hence this method (category association) was chosen for the current study. In addition, our experimental design uses two different probes (category association and word pair association) to cue the same primed words to increase the chances of obtaining an effect. No statistical adjustment was employed for these multiple tests, thus increasing the probability of a type I error but, despite this, we did not obtain significant results.

Other possible factors to consider which could contribute to the lack of recall are the early post-operative testing and the use of temazepam premedication. The effects of temazepam on memory in this situation have not been studied but all patients remembered being in the anaesthetic room and having the epidural catheter inserted, they all remembered the attachment of electronic monitoring electrodes and being taken into the operating theatre and placed on the operating table. In previous studies, temazepam was used as premedication when patients had recall.[7 9] One could argue that the presence of residual temazepam in the immediate post-operative period should increase the probability of recall because of state-dependent memory effects. Our patients were fully responsive to verbal command and conversation at the time of testing and other researchers, using similar testing, found implicit memory when patients were tested 30–179 min after operation.[17] In their meta-analysis, Merikle and Daneman[3] found that early testing was strongly associated with significant implicit memory effects. We believe we tried to favour conditions that would increase the probability of finding evidence for a priming effect.

The most likely reason why we did not find priming is that anaesthesia was adequate. With the IFT we knew whether patients were responsive or not when the information was being played to them. In the majority of memory studies unconsciousness has either been assumed or been determined based on 'normal' clinical signs. In the presence of muscle relaxants, it is difficult to assess the depth of anaesthesia. The usual clinical signs of anaesthesia (heart rate, arterial pressure, sweating, tear production) are unreliable indicators of consciousness during surgery.[18–20] Virtually all the original clinical signs described by Snow[21] and developed by Geudel[22] rely on muscle activity: cardiovascular signs are not mentioned. When muscle relaxants are used, these original clinical signs are of limited, if any, value. The origins of using cardiovascular indices to gauge depth of anaesthesia are unclear and we are not aware of any study which has shown them to be of value in detecting consciousness. On the other hand, several studies using different anaesthetic techniques in conjunction with the IFT have shown clearly that clinical signs cannot be used to predict whether or not patients are awake and responsive during surgery.[7–9 23] In addition, experienced anaesthetists could not distinguish the anaesthetic records of patients known to have suffered awareness with recall from the records of patients with no evidence of awareness and recall.[19]

One previously very widely used anaesthetic technique (nitrous oxide, narcotic, muscle relaxant) may be associated with >50% of patients being awake during surgery but with no conscious recall for this fact after surgery[7] and this anaesthetic technique has been used for all or a large proportion of the patients in some studies of memory and recall which indicate post-operative implicit memory for intra-operative information.[17 24–26] In the meta-analysis by Merikle and Daneman,[3] eight of the nine studies that found evidence for post-operative recall of intra-operative information used an anaesthetic technique based around muscle relaxants (the ninth study did not provide anaesthetic details) and depth of anaesthesia was gauged by clinical monitoring. In the 16 investigations that found no evidence for recall, nine used a relaxant anaesthetic technique, in four the patients breathed spontaneously and in five the anaesthetic technique could not be defined. It is notable that all the spontaneous respiration studies were in the negative outcome group.

In their meta-analysis, Merikle and Daneman[3] concluded that unconscious patients perceive information and remember it after surgery. However, in reaching this conclusion they stated that, 'Despite the remote possibility that some patients may experience moments of awareness during anaesthesia, we believe it is reasonable to assume that patients who are undergoing general anaesthesia are in fact unconscious of all external events for the entire duration of surgery.' The results of IFT studies[7–9 23] indicate that 'the possibility that some patients may experience moments of awareness during anaesthesia' is far from remote and the assumption 'that patients are unconscious of all external events for the entire duration of surgery' cannot be made: with some 'anaesthetic' techniques a significant proportion of patients are awake. This is acknowledged by Andrade,[2] where she points out in the conclusion of her very extensive and exhaustive review of the subject that 'although the studies discussed in this article deal with learning during "clinically adequate" anaesthesia, it is not clear that patients were actually unconscious when stimuli were presented'. Thus while studies in which the IFT has not been used indicate that patients can remember information presented during *surgery*, without direct evidence that patients were adequately anaesthetized, these results cannot be used to indicate recall for information presented during *anaesthesia*.

It is widely accepted that evidence of memory after surgery may reflect moments of intra-operative arousal, but it is still felt that such arousal 'is difficult to prove because there is no practical tool—to predict or identify awareness during anaesthesia'.[27] Lack of knowledge of the conscious state of patients is a fundamental problem when investigating memory and anaesthesia. Why is the IFT (which has been known about for >20 yr) not used to detect awareness during surgery? We believe it may be thought that the technique is unreliable or that studies using the IFT are difficult to interpret because of practical and technical problems.[28] Criticisms of the IFT include the following: (i) response to command using the IFT correlates poorly with clinical signs of light anesthesia;[29] (ii) the IFT can only be used for 20 min as the arm will become paralysed;[12 30] (iii) it is difficult to distinguish purposeful arm movements from reflex movements;[25 28 30–32] (iv) the response to command does not indicate that the patient is conscious;[10 28 30 32 33] and (v) the IFT response does not correlate with recall.[10]

These criticisms represent a fundamental misunderstanding of the IFT which has been discussed in detail.[11 23] If a patient responds to commands during surgery, then this is a clear indication that the patient is not unconscious—irrespective of the clinical signs. In these circumstances it is the clinical signs which are unreliable, not the IFT. It is precisely for this reason that the IFT has been described as the gold standard for assessing consciousness during general anaesthesia in the presence of muscle relaxants.[10]

The 20 min limit on the use of the IFT is a widespread misconception and arises from a belief that the 20 min limit for inflation of the tourniquet is the end of the IFT. If doses of muscle relaxant are selected carefully, there is no time limit to the duration of the IFT.[11 23] Table 7 shows that there is no 20 min limit on the use of the IFT.

The criticism that it is difficult to distinguish between reflex and purposeful movements of the arm is based entirely on two studies where no attempts were made to distinguish between these two types of movement: movements of the hand were merely observed.[25 31] The two types of hand movement can be readily distinguished by directly asking the patient to respond in a particular manner.[11 23 34]

The definition of consciousness has been much debated but, in simple terms, we do not believe that a patient responding to conditional commands during surgery can be described as unconscious.

It is true that IFT responses do not correlate well with recall, but this is to be expected. It is well recognized in volunteer studies using nitrous oxide,[35] isoflurane[36] or propofol[37] that subjects under the influence of low doses of these drugs may be conscious and responsive to commands yet, later, have no explicit or implicit memory for these commands. When using the IFT during surgery, most patients begin to respond to commands at a level of consciousness where the information is either not stored in memory or is stored in such a manner that it cannot be recalled after surgery. The exact conditions required for memory to be stored in a retrievable manner are not known, but it is possible that memory will start to be 'laid down' if anaesthesia continues to lighten or if there is a period of more intense surgical stimulation while the patient is responding.

The studies of Jelicic and colleagues[24 38] show the difference between an inadequate and an adequate anaesthetic technique on the results of identical memory studies. With a relaxant–nitrous oxide–narcotic technique, where there is a high probability of patients being awake and responsive during surgery,[7] these authors found good evidence of post-operative recall for information presented during surgery.[24] However, when the same testing methodology was used with a volatile anaesthetic technique and spontaneous respiration, where the likelihood of patients being awake during surgery is very low, they found no evidence of recall.[38]

None of the seven women in the current study who responded to commands during surgery showed evidence of explicit or implicit memory. Since propofol abolishes recall in conscious volunteers, [39 40] this finding is not surprising. These seven women had effective epidural anaesthesia and surgical stimuli would not heighten their arousal. The effect of the epidural analgesia on the incidence of responsiveness can be compared with the results of 12 women for whom data have not been presented above. These 12 women consented to the memory investigation aspects of this study but then refused epidural analgesia. Five of these 12 women (42%) awoke at propofol infusion rates between 8 and 4 mg kg^{-1} h^{-1} (the propofol/alfentanil solution in these 12 patients consisted of propofol 500 mg mixed with alfentanil 5000 µg to a total volume of 60 ml[14]). Thus the overall incidence of intra-operative wakefulness in all 52 patients was 21%, with none having post-operative recall. This compares with the rate of 0.2% for post-operative recall of intra-operative events found by Nordstrom and colleagues,[14] after post-operative interviews with 1000 patients anaesthetized with an almost identical technique. These authors[14] concluded that 'if the true incidence of conscious awareness is to be determined, interviews must be extended beyond the first post-operative day'. However, these authors were detecting recall, not conscious awareness. Comparison of the present study with that of Nordstrom and colleagues[14] shows that there may be a wide difference in the incidence of intra-operative wakefulness and post-operative recall for that wakefulness. To date, wakefulness during surgery can only be reliably detected with the IFT.[11]

In conclusion, we found explicit or implicit memory of information presented during surgery under total intravenous anaesthesia with propofol and alfentanil, either when anaesthesia is sufficient to maintain patients in an unresponsive state or for short periods of responsiveness. Even when using an anaesthetic technique with a reliably estimated incidence of post-operative recall of 0.2%,[14] the importance of using the IFT to detect intra-operative wakefulness is clearly shown. These results support the argument that when investigating post-operative memory for information presented while patients are anaesthetized, evidence must be provided that anaesthesia was adequate.

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Psychomotor recovery in very old patients after total intravenous or balanced anaesthesia for cataract surgery

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We compared psychomotor recovery after total intravenous anaesthesia (TIVA) with remifentanil/propofol and balanced anaesthesia (BAL) with etomidate/fentanyl/isoflurane in 40 patients, ASA I–III, aged ≥80 yr undergoing elective cataract surgery. Recovery times were recorded and psychomotor recovery was assessed according to simple reaction time, critical flicker fusion frequency (CFF) and short-term memory 30 min, 2 h and 1 day after surgery. Physical characteristics of patients in the two groups (19 in the TIVA group and 21 in the BAL group) were comparable. The TIVA group recovered significantly more quickly. Both groups showed a poorer psychomotor performance 30 min after surgery than at baseline assessment, but simple reaction time and short-term memory were close to baseline values 2 h after surgery. Only performance in the CFF test remained below baseline at this point. No deficits in psychomotor performance were noted on the first day after surgery. We conclude that there is only a minor deficit in psychomotor function in elderly patients 2 h after cataract surgery under general anaesthesia and that psychomotor function recovers completely by 24 h after surgery.

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Life expectancy has increased considerably over the last few decades and, accordingly, so has the proportion of elderly patients requiring surgery and anaesthesia. Simultaneously, an increasing number of surgical procedures is performed on an outpatient basis. In order to avoid delays in the postanaesthesia care unit (PACU) and in the time to discharge after outpatient anaesthesia, fast and predictable recovery of cognitive function is of major importance. It is particularly a matter of concern in aged patients, as the morphological and physiological changes in the brain related to ageing have to be taken into consideration. It is known that in elderly patients the required dose of certain anaesthetics is lower.[1 2] However, little is known about how recovery of cognitive function is affected by anaesthesia in elderly patients.

We investigated the effect of total intravenous anaesthesia (TIVA) with remifentanil and propofol and BAL with fentanyl and isoflurane on psychomotor recovery in patients aged ≥80 yr. Here we present a subgroup analysis of a clinical trial with pharmacoeconomic endpoints in which 124 patients (aged ≥65 yr) were enrolled. The results of this study have been accepted for publication elsewhere.[3]

Subjects and methods

Anaesthesia

Following institutional review board approval, 40 patients aged ≥80 yr, ASA physical status I–III, undergoing elective cataract surgery under general anaesthesia were included in this single-blind study. All patients gave written informed consent. Prospective patients with a history of an allergic reaction to one of the drugs used in this study were ineligible for participation. A computer-generated randomization schedule was used to assign patients randomly to receive either TIVA with remifentanil and propofol or BAL with fentanyl and isoflurane.

In order to avoid any effects of premedication on the postoperative psychomotor test results, none of the patients received sedative drugs as premedication. A peripheral intravenous cannula was placed for drug and fluid administration and standard monitoring—comprising pulse oximetry, automated arterial pressure cuff measurements and electrocardiogram—was applied. Subjects were monitored for systolic and diastolic arterial pressure, heart rate and haemoglobin oxygen saturation throughout surgery and the recovery period. Before induction of anaesthesia, all

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Table 1 Words used in the short-term memory test (translated from German)

Time	Words used in test
Preoperatively	flower, street, plate, day, bed
30 min	apple, book, cup, moon, spoon
120 min	grass, knife, picture, cake, light
1 day	earth, chair, time, glass, glasses

patients were preoxygenated for 2 min. In the TIVA group, anaesthesia was induced with propofol 1.5 mg kg^{-1} and remifentanil 1 μg kg^{-1} over a 3 min period. In the BAL group, subjects received etomidate 0.1–0.3 mg kg^{-1} and fentanyl 1.5 μg kg^{-1} for induction of anaesthesia. Approximately 3 min after starting anaesthesia, mivacurium 0.15 mg kg^{-1} was administered in both groups to achieve muscle relaxation. After tracheal intubation, all patients were ventilated mechanically to normocapnia with oxygen-enriched air ($F_{I_{O_2}}$=0.4) and a constant fresh gas flow of 3 litres min^{-1}. Anaesthesia was maintained by a continuous infusion of propofol 0.05–0.1 mg kg^{-1} min^{-1} and remifentanil 0.15–0.3 μg kg^{-1} min^{-1} in the TIVA group and with isoflurane 0.8–2.5 MAC and a bolus of fentanyl 0.1 mg at the beginning of surgery in the BAL group. Infusion rates and MAC were adjusted, if necessary, to achieve an adequate depth of anaesthesia and to provide haemodynamic stability. Hypotension and bradycardia were treated with sympathomimetic and anticholinergic drugs, respectively, following institutional guidelines.

At the end of surgery, anaesthesia was stopped and the patients' lungs were ventilated manually with 100% oxygen. After adequate respiration had been resumed and the patients were able to open their eyes on command, the trachea was extubated and patients were transferred to the PACU, where monitoring of vital signs was continued.

The duration of surgery and anaesthesia was recorded. Recovery was assessed by recording the time to respond to verbal commands (open eyes) and extubation. The Aldrete score[4] was recorded upon arrival in the PACU and every 15 min thereafter until the patients achieved a score of ≥9. The score includes five tasks that assess muscle activity, respiratory efficiency, changes in systolic arterial pressure from the preanaesthetic level, consciousness and skin colour. The maximum score is 10.

Recovery testing

Psychomotor and cognitive function tests used during the study included: simple visual reaction time, simple auditory reaction time, critical flicker fusion frequency (CFF) and short-term memory. These tests have been used in a similar way in previous studies and are considered suitable for detecting even minor impairment of psychomotor function.[5 6] They are easy to use and are not time consuming, which is an important factor in psychomotor testing in the early postoperative period.

Simple reaction time

To evaluate the simple visual reaction time, the patient was instructed to press a button when a red light of about 3 cm diameter, placed approximately 80 cm from the eyes, was illuminated. In the test of simple auditory reaction time, the red light was replaced by an auditory stimulus, which could easily be heard by the patient, as verified before the start of the test. Each test was performed three times per session; mean results (expressed in seconds) were recorded.

CFF

In this test, the patient was shown a flickering red light, which was of the same diameter and placed at the same distance as the one used for the simple visual reaction time. Its flicker frequency was slowly increased and the patient was instructed to report as soon as the light appeared to be continuous. The test was performed three times per session; the mean results, expressed in hertz, were recorded.

Short-term memory test

In the short-term memory test, patients were asked to memorize five words, which were read to them twice and which they had to repeat once in order to exclude communication problems. After 2 min, in which patients had to fill in a concentration test in order to distract them from constantly repeating the given words, they were asked to recall those five words and the number of correctly recalled words was recorded. Different words were used in each session (Table 1).

In addition to these tests, a visual analogue scale (VAS) was used to evaluate the intensity of sedation. According to this scale, a score of 0 represented no sedation/totally awake and a score of 100 represented the deepest sedation imaginable. At each time point, patients were asked to move the pointer on the VAS to the place where they considered their sedation to be most accurately represented. The numerical equivalent was noted by the observer. Patients feeling too drowsy to perform this test were not given a value.

On the evening before anaesthesia, the patients were familiarized with this series of tests and the VAS and baseline values were obtained. The tests and the VAS were repeated 30 min, 120 min and 1 day after the end of surgery, and were always carried out by the same observer.

In addition to the assessment of each psychomotor test, we wanted to evaluate test compliance, defined as the ability and willingness to perform the complete series of tests at the given time points. Patients were always asked to perform the tests but the decision to do so was ultimately their own.

Statistical analysis

Patient characteristics were compared using the χ^2 test and Student's *t*-test. Recovery times, atropine requirements, VAS results and between-group differences in the psychomotor recovery tests were analysed with two-way analysis of variance (ANOVA). Psychomotor recovery test results

Table 2 Physical characteristics and recovery times (mean (SD)). ns, not statistically significantly different

	TIVA (*n*=19)	BAL (*n*=21)	*P* value
Age (yr)	84.5 (80–89)	83.2 (80–88)	ns
Gender (male/female)	12/7	16/5	ns
ASA physical status I/II/III (*n*)	0/13/6	0/9/12	ns
Duration of surgery (min)	27.6 (12.0)	28.6 (12.1)	ns
Time (min) to			
Extubation	7.0 (3.0)	13.8 (5.8)	<0.01
Eye opening	7.0 (2.9)	15.9 (5.7)	<0.01
Aldrete score ≥9	11.5 (8.1)	39.8 (26.3)	<0.01

Table 3 Test compliance (number of patients who participated in psychomotor testing at the given time points); *significant difference between the TIVA and BAL groups ($P<0.01$)

	TIVA (*n*=19)	BAL (*n*=21)
Preoperatively	19	21
30 min	18	11*
120 min	16	18
1 day	16	20

were further analysed with Student's paired *t*-test for comparison between preoperative and postoperative values. Fisher's exact probability test was used for comparison of test compliance. For all statistical tests, a two-sided *P*-value of <0.05 was considered statistically significant.

Statistical analysis was performed using SPSS version 6.0.1. Data are expressed as mean (SD) unless stated otherwise. For simple reaction time and CFF tests, postoperative results are presented as mean changes (SD), i.e. the difference between the mean baseline value and the mean postoperative value at the given time point.

Results

Forty ASA class II–III patients were enrolled in this study. The two study groups were similar with respect to physical characteristics and duration of surgery (Table 2). However, immediate recovery, as assessed by times to awakening and to meeting the Aldrete recovery criteria[4] (score ≥9), differed between the two groups, with significantly shorter times being observed in the TIVA group (Table 2). One subject in the TIVA group had a myocardial infarction on the day after surgery and was excluded from the analysis at this time point. The patient was transferred to the cardiac intensive care unit, where coronary arteriography showed three-vessel disease.

In the TIVA group, atropine was administered for treatment of bradycardia in 18 of the 19 patients, whereas only 12 of the 21 patients in the BAL group received atropine. The mean dose of atropine differed significantly ($P=0.003$) between the two groups (0.55 mg in the TIVA group and 0.25 mg in the BAL group).

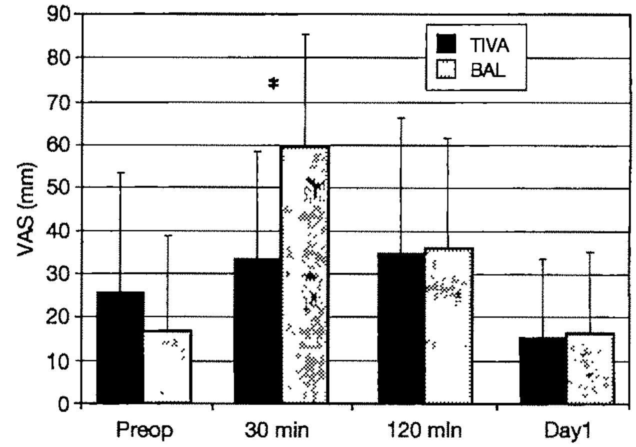

Fig 1 Visual analogue sedation scores (mean ± SD). $^*P<0.01$; TIVA versus BAL.

There was a significant difference between groups with respect to the ability to complete the testing session 30 min after surgery. Eighteen of the 19 patients in the TIVA group completed the whole series of tests at that time, whereas only 11 of 21 patients in the BAL group did so. However, 120 min after surgery and on the day after surgery, test compliance between the groups was comparable (Table 3). Common reasons for omitting psychomotor testing were feeling sleepy or drowsy, nausea, vomiting or simply 'not being in the mood to do the test series for unknown reasons'. The latter was the main reason why more patients in the TIVA group did not perform the psychomotor tests 120 min and 1 day after surgery, although they were considered capable of doing so by the observer.

The results of the VAS are presented in Figure 1. In the TIVA group, 18 of 19 patients completed the VAS 30 min after the end of surgery, whereas only 14 of 21 in the BAL group did so. Patients in the TIVA group had significantly lower sedation scores than patients in the BAL group at this time point. In both groups, patients felt significantly more tired at the time points 30 min and 120 min postoperatively compared to the preoperative value, but on the first postoperative day sedation scores did not differ from baseline values.

The results of the simple reaction time tests, the CFF and short-term memory test are shown in Table 4. Thirty minutes after the end of anaesthesia, both visual and auditory reaction times were significantly longer than baseline in both groups, but there were no differences from baseline 2 h and 1 day after the end of anaesthesia. A significant between-group difference was observed in the mean change in auditory reaction time 30 min after surgery ($P=0.04$). At this time point, auditory reaction time was significantly shorter in the TIVA group. However, there were no between-group differences in mean change in reaction time at any of the other time points.

The results of the CFF showed a minor psychomotor impairment in both groups for 2 h following surgery. In

Table 4 Results of psychomotor tests. For each test, data are expressed as mean changes (SD); *n*=number of patients. *Significantly different from pre-operative value ($P<0.05$); #significantly different from pre-operative value ($P<0.01$)

	TIVA		BAL		P value for
	n	Mean (SD)	*n*	Mean (SD)	TIVA vs BAL
Visual reaction time (s)					
Preoperative value	19	0.36 (0.14)	21	0.38 0.20)	0.682
Mean changes in visual reaction time (s)					
30 min	18	0.07* (0.09)	12	0.12* (0.07)	0.139
120 min	17	0.02 (0.09)	19	0.03 (0.21)	0.966
1 day	16	–0.02 (0.13)	20	0.00 (0.15)	0.630
Auditory reaction time (s)					
Preoperative value	19	0.36 (0.25)	21	0.33 (0.12)	0.408
Mean change in auditory reaction time (s)					
30 min	18	0.09* (0.12)	12	0.24* (0.25)	0.04
120 min	17	0.02 (0.09)	20	–0.03 (0.15)	0.249
1 day	16	–0.01 (0.07)	20	–0.10 (0.18)	0.073
CFF (Hz)					
Preoperative value	19	36.9 (3.8)	21	38.4 (4.5)	0.266
Mean change in CFF (Hz)					
30 min	18	3.12# (2.20)	11	2.45* (4.07)	0.580
120 min	16	2.87* (4.03)	18	3.86* (4.72)	0.530
1 day	16	2.89 (3.11)	20	1.65 (3.95)	0.324
Short-term memory (number of correctly recalled words):					
Preoperative value	19	3.5 (1.3)	21	3.2 (0.6)	0.846
30 min	18	2.7 (1.3)	11	2.3 (1.)	0.462
120 min	17	2.7 (1.6)	19	2.3 (1.3)	0.744
1 day	16	3.5 (1.2)	20	3.2 (1.6)	0.880

both groups, the CFF remained significantly lower than baseline 30 min and 120 min after the end of anaesthesia, but did not differ significantly from baseline on the first postoperative day. At no time point were differences between the groups in mean changes of CFF noted.

In both groups, performance in the short-term memory test was slightly, but not significantly, decreased 30 min and 2 h after the end of anaesthesia as compared with baseline. On the first day after surgery, the mean number of correctly recalled words was identical to baseline values for both groups.

Discussion

In this study we investigated psychomotor recovery in the early post-operative period in very elderly patients undergoing cataract surgery under general anaesthesia. Cataract surgery, a minimally invasive procedure, serves as a model to focus on the effects of general anaesthesia on recovery of psychomotor function in that other factors that might have an effect after major surgery, such as blood loss, hypercapnia, hypoxaemia and postoperative pain, are eliminated or reduced to a minimum. Carbon dioxide partial pressure and oxygen saturation were not noted, but with the ventilation pattern used in this study we assumed that they remained within the physiological range and did not differ among the study groups. The decision as to whether surgery was performed under local or general anaesthesia in a patient eligible for randomization depended on the patient's and surgeon's preferences.

Recovery from anaesthesia in aged patients was quicker after TIVA with remifentanil and propofol than after BAL with fentanyl and isoflurane, which is related to the different pharmacokinetic characteristics of the two opioids. In this study, the time to extubation after remifentanil/propofol anaesthesia was similar to that in younger adults observed in previous studies.[7–9] Suttner and colleagues[8] and Hogue and colleagues[9] reported a time to extubation of 6 min and 7 min, respectively, in adult patients. However, Hogue and colleagues[9] reported a time to first Aldrete score ≥9 of 20 min and 23 min depending on the remifentanil dose in adults ≥18 yr undergoing inpatient surgery. The shorter time taken to reach an Aldrete score of ≥9 in this study might be explained by the smaller requirements for anaesthetic drugs during cataract surgery. Recovery after fentanyl/isoflurane anaesthesia in the elderly subjects studied was prolonged and time to extubation and to eye opening was approximately 7 min longer than in non-geriatric adults who were extubated and able to open their eyes 7 and 9 min, respectively, after the end of anaesthesia (compared with 14 and 16 min in the present study).[10] Suttner and colleagues,[8] however, reported in ordinary adults a time to extubation similar to the one in this report.

With respect to the early post-operative period, we found that psychomotor recovery in very old patients was significantly impaired after both anaesthetic techniques 30 min after the end of anaesthesia, but 2 h post-operatively psychomotor function was close to the baseline value. Only sedation scores and performance in the CFF test differed significantly from baseline 120 min post-operatively, but the simple reaction times and short-term memory test were the same as preoperative values. The fact that a greater proportion of patients in the TIVA group felt able to complete the VAS 30 min after the end of surgery suggests that the difference in sedation between the groups was even greater than found in this study. The CFF has been considered to be one of the most sensitive tests for detecting psychomotor dysfunction caused by psychoactive drugs;[5] our results suggest that a very slight impairment of psychomotor function remains 2 h postoperatively. No psychomotor deficit was found on the day after surgery.

There were fewer between-group differences than expected considering the very different pharmacokinetic characteristics of the two opioids used in this study. The more frequent administration and higher dose of atropine (which has been suspected of causing cognitive deficits[11]) in the TIVA group may be partly responsible. The lower test compliance observed in the BAL group seems to be related both to the comparatively high incidence of postoperative nausea and vomiting in this group, as described by Green and Jonsson,[12] and the prolonged sedative effects of fentanyl. Considering the test compliance and simple auditory reaction time results 30 min after the end of surgery, TIVA with remifentanil and propofol seems to have advantages over BAL with fentanyl and isoflurane in relation to recovery of postoperative psychomotor function.

Data on psychomotor recovery in aged patients in the early postoperative period after general anaesthesia are comparatively scarce. This is one of the first studies to investigate it and therefore the comparability of the psychomotor test results presented here with those of previous studies is limited. Our findings are similar to those of Moffat and Cullen,[13] who reported that cognitive mental function in patients aged >60 yr is close to preoperative values 2 h after general anaesthesia with propofol or etomidate–vecuronium–isoflurane for day-case cataract surgery. However, early or short-term postoperative cognitive function was found to be impaired after major surgery in elderly patients.[14 15] In a study by Keita and colleagues,[16] cognitive function in elderly patients undergoing elective orthopaedic surgery under propofol–alfentanil anaesthesia did not return to preoperative values within the first 2 h after surgery whereas younger patients showed the same test performance as they did before surgery at that time. In a multicentre study in which 1218 patients scheduled for major non-cardiac surgery were enrolled, Moller and colleagues[17] demonstrated postoperative cognitive dysfunction in 25.8% of patients 1 week after surgery and in 9.9% of patients 3 months after surgery. Williams-Russo and colleagues[18] found no differences in neuropsychological test performance between general and regional anaesthesia 1 week and 6 months after orthopaedic surgery, but that 5% of patients had impaired cognitive function 6 months after surgery. It is likely, therefore, that the reason why patients in the present study did not show impaired postoperative psychomotor function 1 day after surgery is related to the minimally invasive character and short duration of cataract surgery, which has been found to be related to early postoperative cognitive dysfunction.[17]

Within the confines of the psychomotor test battery used in this study, we conclude that there is only a minor postoperative deficit in psychomotor function in elderly patients 2 h after the end of general anaesthesia with remifentanil and propofol or fentanyl and isoflurane given for cataract surgery, and that there is no psychomotor dysfunction 1 day after the end of anaesthesia. Our results suggest that psychomotor function recovers more quickly after TIVA with remifentanil and propofol than after BAL with fentanyl and isoflurane.

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EEG bispectral index and hypnotic component of anaesthesia induced by sevoflurane: comparison between children and adults

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This prospective study was designed to evaluate the correlation between the electroencephalographic bispectral index (BIS) and the hypnotic component of anaesthesia (CA) induced by sevoflurane in 27 children and 27 adult patients. BIS and CA were compared at loss of consciousness (LOC) and on recovery of consciousness (ROC). Mean (SD) BIS decreased significantly at LOC in children and adults from 94 (2.7) to 87.4 (4) and from 96.2 (2) to 86.7 (4.4), respectively, without any difference between groups. Correlation coefficients (ρ) between BIS and CA at LOC were –0.761 in children and –0.911 in adults. BIS increased significantly at ROC in children and adults from 74.1 (4.2) to 86.7 (2) and from 80.2 (5) to 90.7 (3), respectively, without any difference between groups. Correlation coefficients between BIS and CA in ROC were –0.876 in children and –0.837 in adults. BIS values at ROC were not different from those at LOC in either group. These data demonstrate that BIS correlates with the hypnotic component of anaesthesia induced by sevoflurane in children as well as in adults.

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The electroencephalographic (EEG) bispectral index (BIS) has been shown to be a quantifiable measure of the hypnotic effect of anaesthetic drugs on the central nervous system.[1 2] The potential usefulness of BIS monitoring as an indicator of the depth of hypnosis during inhalation anaesthesia,[3 4 5] particularly during sevoflurane sedation, has been described.[6 7] Previous studies that evaluated BIS were performed in adults not children. Sevoflurane is well tolerated[8] in terms of airway complications (causing minimal breath-holding, coughing, excitement or laryngospasm), with minimal changes in haemodynamics; it is used in adults and children for rapid induction of anaesthesia.[9 10]

This prospective study was designed to evaluate the correlation between BIS and the clinically assessed hypnotic component of anaesthesia (CA score) in children and adults patients when sevoflurane is used as the sole anaesthetic.

Methods

After obtaining institutional review board approval and written, informed consent from the patients or their parents, 54 ASA I patients scheduled for tympanoplasty were assigned to one of two groups designated as child (*n*=27) or adult (*n*=27).

All patients were admitted on the day before surgery and fasted for at ⩾12 h before their operation. All patients received oral premedication (hydroxyzine 1 mg kg^{-1}, alprazolam 0.015 mg kg^{-1}) 2 h before surgery. On arrival in the operating room, in addition to routine monitoring (heart rate (HR), non-invasive mean arterial pressure (MAP), pulse oximetry), the EEG signal was acquired using four Zipprep electrodes (Aspect Medical Systems, Natick, MA) applied to the forehead, with one on the outer aspect of each malar bone and one at the centre of the forehead, and the ground electrode above the central electrode. The BIS value was displayed using an Aspect EEG monitor (Model A-1000; Aspect Medical Systems). A 24- (for children) or 18-gauge catheter (for adults) was inserted into a forearm vein and used for administration of fluid and drug. A 5% glucose solution (for children) or Ringer's solution (for adults) was administered at 5 ml kg^{-1} h^{-1}. Baseline values for BIS and haemodynamic variables were obtained, and then all patients breathed through a face mask connected to a

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Table 1 Hypnotic component of anaesthesia (CA) score

Responsiveness	**Score**
Responds readily to name spoken in normal tone	0
Lethargic response to name spoken in normal tone	1
Responds only after name is called loudly	2
Responds only after mild prodding or shaking	3
Responds only after painful trapezius squeeze	4
Does not respond to painful trapezius squeeze	5

Table 2 Patient characteristics and duration of anaesthesia (mean (SD) or (for gender) distribution)

	Children (n=27)	**Adults** (n=27)
Age (yr)	8.6 (3.5–13)	39.5 (22–72)
Gender (female/male)	11/16	13/14
Weight (kg)	29.5 (11.3)	72.6 (9.8)
Duration of anaesthesia (min)	62 (30)	125 (47)

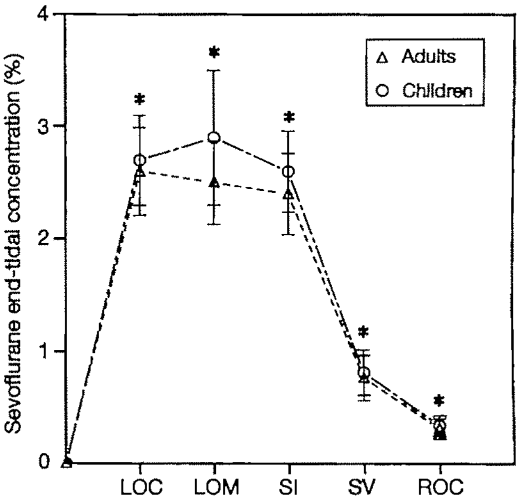

Fig 1 End-tidal concentrations of sevoflurane in child and in adult patients (27 in each group). LOC, loss of consciousness; LOM, loss of movement; SI, skin incision; SV, spontaneous ventilation; ROC, recovery of consciousness. Data are post-stimulus (see Table 1) values. Results are mean±SD. *Significantly different from baseline values in each group (P<0.05); one-way analysis of variance with Bonferroni's correction.

semiclosed anaesthetic circuit. Fresh gas flow into the anaesthetic circuit was 6 litres min^{-1}.[7] The concentrations of carbon dioxide, sevoflurane and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac, Helsinki, Finland), which was calibrated before anaesthesia for each patient using a standard gas mixture. Anaesthesia was induced with 4% sevoflurane in oxygen; ventilation was assisted as necessary. The inspired concentration of sevoflurane was adjusted to obtain loss of consciousness (LOC) and loss of movement. The end-tidal carbon dioxide concentration was kept between 4.67 and 5.34 kPa during the study period. Just after loss of movement and before tracheal intubation, children and adults received a bolus of alfentanil 25 μg kg^{-1} i.v. followed by a constant infusion of 0.5 μg kg^{-1} min^{-1}. Tracheal intubation was performed after 5% lidocaine local anaesthetic had been applied to the glottis. The BIS and hypnotic component of anaesthesia (CA score) were evaluated during the onset of sevoflurane-induced anaesthesia, i.e at LOC, every 15 s until loss of movement occurred, and on recovery of consciousness (ROC). During the onset and offset periods, the CA score was assessed clinically by using the responsiveness component of the observer's assessment of alertness/sedation (OAA/S) rating scale (Table 1). From LOC until ROC, BIS was recorded continuously. The end of the recovery period was defined as the time when a patient opened their eyes on verbal command (CA=2). During surgery, sevoflurane concentrations were adjusted according to standard clinical practice to maintain haemodynamic stability and avoid patient movement, with the aim of achieving rapid recovery after surgery.

One-way analysis of variance (ANOVA) was performed for comparison of all continuous variables between groups; when indicated, a Bonferroni's correction was performed for *post hoc* comparisons within and between groups. The relationship between BIS and CA score was evaluated at LOC and ROC using non-parametric Spearman's correlation analysis. Data are expressed as mean (SD). P values of <0.05 were considered statistically significant.

Results

Patient characteristics and duration of anaesthesia are shown in Table 2. End-tidal concentrations of sevoflurane during onset of LOC and on recovery were not significantly different between the two groups (Figure 1). With increasing depth of anaesthesia from a CA score of 0 to 5, the BIS decreased significantly from 94 (2.7) in children and from 96.2 (2) in adults to 87.4 (4) (P<0.05) and 86.7 (4.4) (P<0.05), respectively, in the onset period (Table 3). BIS increased significantly from 74.1 (4.2) in children and from 80.2 (5) in adults to 86.7 (2) (P<0.05) and 90.7 (3) (P<0.05), respectively, as the CA score decreased from 5 to 2 in the recovery period (Table 4). BIS values were comparable in the two groups at each time point (Figure 2). Within the two groups, there was no difference between BIS values at LOC and those at ROC. BIS values were inversely correlated with CA scores at LOC in children (Spearman's ρ –0.761) and adults (Spearman's ρ –0.911), and at ROC in children (ρ –0.876) and adults (ρ –0.837).

Discussion

The main finding of this study was that the EEG BIS correlated with the hypnotic component of anaesthesia induced by sevoflurane in children and in adults. A significant correlation was demonstrated between BIS and CA score during onset of and recovery from sevoflurane-

Table 3 Changes in BIS during the onset of sevoflurane-induced anaesthesia (ANOVA= analysis of variance; *significantly different from a CA score of 0 ($P<0.05$))

CA score	BIS index		ANOVA
	Children (n=27)	Adults (n=27)	(Bonferroni)
0	94 (2.7)	96.2 (2)	NS
1	93.4 (3)	93 (3.1)	NS
2	93.1 (3.2)	91 (2)	NS
3	91 (5)	90 (2)	NS
4	89 (3)	89.3 (4.2)	NS
5	87.4 (4)*	86.7 (4.4)*	NS

Table 4 Changes in BIS during recovery from sevoflurane-induced anaesthesia (ANOVA=analysis of variance; *significantly different from a CA score of 5)

CA score	BIS index		
	Children (n=27)	Adults (n=27)	ANOVA (Bonferroni)
5	74.1 (4.2)	80.2 (5)	NS
4	80.7 (3)	83.3 (3)	NS
3	82.3 (2)	85.6 (3)	NS
2	86.7 (2)*	90.7 (3)*	NS

induced anaesthesia. An increasing CA score was associated with a decrease in BIS, whereas a decreasing CA score was associated with an increasing BIS.

In this work, adults served as a control group for children as no studies have been done in children to our knowledge. Many studies in adults have demonstrated the ability of the BIS to define depth of sedation induced by sevoflurane[7] or its ability to predict patient movement in response to skin incision during isoflurane[11] or propofol–nitrous oxide anaesthesia.[12 13] In our study, the CA score did not include the motor response to noxious stimuli. At present, it is not acceptable to include movement in the assessment of depth of anaesthesia and to correlate it with BIS; EEG BIS is a form of cortical function monitoring which cannot predict a response to noxious stimuli mediated by subcortical structures.[7] Cortical activity does not accurately predict motor response to noxious stimuli.[3 14] Cortical and subcortical (motor, haemodynamic and endocrine stability) components of anaesthetic 'adequacy' are independent of each other. For educational purposes, when it is compared with BIS, depth of anaesthesia should be referred to as the 'hypnotic component of anaesthesia'. For this reason, in this study, BIS values were not compared with CA scores during surgery, and were only recorded to compare the two groups. Even though the BIS cannot predict directly motor response to noxious stimuli, it can serve in clinical practice as an indicator of depth of anaesthesia as defined by its hypnotic component, for lack of a more specific one. The hypnotic component of anaesthesia can be defined by a threshold of amnesia, beyond which intraoperative recall disappears.

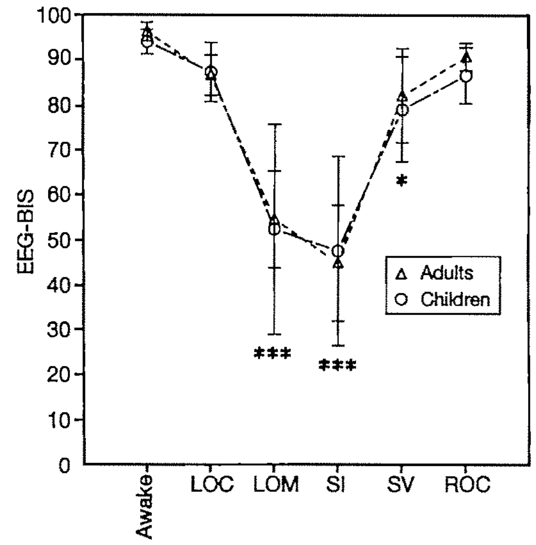

Fig 2 EEG BIS in child and adult patients (27 in each group). Abbreviations as in Figure 1. Awake=baseline values. Data are post-stimulus (see Table 1) values. Results are mean±SD. ***Significantly different from baseline values within group ($P<0.001$); one-way analysis of variance with Bonferroni's correction where indicated.

During propofol-induced sedation[2], none of the patients were able to recall pictures shown during the operation at an OAA/S score of 2, with a corresponding BIS of 80.8 (8.3) (mean (SD)). In the present study, the threshold of amnesia would correspond to a CA score of 3. Further studies are necessary in order to assess the relationship between intraoperative recall and BIS during sevoflurane-induced sedation and anaesthesia. In this study, when using sevoflurane during a monitored anaesthetic technique, the anaesthetist attempted to titrate the drugs to optimize patient comfort, while maintaining cardiorespiratory stability. Further studies are needed to determine whether it will be possible to improve the administration of sevoflurane by using BIS monitoring as an adjunct to routine clinical assessment. Meanwhile, these results inform anaesthetists of the BIS value at which LOC and loss of movement occur in anaesthetized children or adults, allowing adjustment of the sevoflurane concentration to avoid undesirable recall[2] or movements, and to predict recovery of consciousness if BIS is used.[15] Stable anaesthetic concentrations of sevoflurane could not be obtained in this study during onset of sevoflurane-induced anaesthesia in children because of the excitation period that prohibits noxious stimulation.

The dynamic relationship between end-tidal sevoflurane concentration and BIS has been evaluated.[16 17] Liu and colleagues[18] showed that, with increasing sedation with benzodiazepines, there was a progressive decrease in BIS. In the present study, a sedative premedication with a benzodiazepine was given orally 2 h before anaesthesia in both children and adults, ensuring stable sedation at the time of measurement of the baseline values of BIS and CA score. These were at satisfactory high levels in both groups, which shows that premedication did not disturb the level of consciousness. It has already been shown that benzodiazepines do not shorten the time taken to achieve LOC with inhalational anaesthetic induction with sevoflurane.[19] The pharmacokinetic properties of sevoflurane,[8] i.e. rapid washout from body tissues and low blood–gas partition coefficient, facilitate control over the depth of anaesthesia, and a rapid and smooth induction of, and emergence from, anaesthesia. This explains why the duration of administration of this potent inhalational agent has little effect on BIS and the depth of anaesthesia at the time of ROC. Moreover, in the present study, although duration of surgery was twice as long in adults as in children, there was no significant difference between the two groups in BIS and CA score at the time of ROC.

In summary, the EEG BIS correlated with the hypnotic component of anaesthesia induced by sevoflurane in children and adult patients.

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British Journal of Anaesthesia **86** (2): 213–16 (2001)

Sevoflurane EC_{50} and EC_{95} values for laryngeal mask insertion and tracheal intubation in children

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The laryngeal mask airway (LMA†) is a simple, easy to use and safe method for airway control in children. Its insertion needs less anaesthetic, and haemodynamic responses and post-operative sequelae are less than with laryngoscopy and tracheal intubation. This study was designed to determine the end-tidal concentrations of sevoflurane where 50% (EC_{50}) and 95% (EC_{95}) of the attempts to secure the airway would be successful. We randomly assigned 40 children aged 4–12 yr undergoing general surgery to either LMA insertion (*n*=20) or to laryngoscopy and tracheal intubation (*n*=20) under sevoflurane anaesthesia. The initial end-tidal concentration of sevoflurane for each child was determined according to the response of the previous child in the same group. Up to three attempts to secure the airway with increasing sevoflurane end-tidal concentrations in 0.3% steps were allowed for each child. The logistic regression model was used to calculate the EC_{50} and EC_{95} values. Sevoflurane provided good conditions for both LMA insertion, and laryngoscopy and tracheal intubation without serious adverse effects. The EC_{50} and the EC_{95} of sevoflurane were 1.57 (SD 0.33)% and 2.22% for LMA insertion and 2.20 (SD 0.31)% and 2.62% for laryngoscopy and tracheal intubation. Thus, less sevoflurane is required for LMA insertion in children than for laryngoscopy and tracheal intubation.

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The laryngeal mask airway (LMA†) is widely used for anaesthesia in children. Compared with laryngoscopy and tracheal intubation, it is easy to use, causes less haemodynamic response to insertion and removal, and fewer complications such as coughing and sore throat.[1] Less sevoflurane seems to be required for LMA insertion than for laryngoscopy and tracheal intubation.[2] In patients with upper respiratory tract infection it seems to cause less bronchoconstriction than the tracheal tube.[3–5]

Previous studies have only assessed the concentration where 50% of the attempts to secure the airway have succeeded (effective concentration EC_{50}).[2 6 7] We designed a study to determine both the EC_{50} for LMA and laryngoscopy and tracheal intubation, and also the concentration where 95% of the attempts would succeed (EC_{95}).

Materials and methods

We obtained ethics committee approval, written informed consent from the parents, and assent from children aged 7 yr or older, from 40 healthy children undergoing elective surgery under general anaesthesia (see Table 1 for patient characteristics). We excluded patients with a history of significant cardiorespiratory, renal or hepatic dysfunction or concurrent treatment with medication known to affect anaesthetic requirements, if the weight of the patient exceeded 150% of the ideal weight, or if the patient had symptoms of upper respiratory tract infection. The child was excluded from the study if premedication was needed after randomization and obtaining informed consent.

The children were randomly allocated either to LMA insertion or to laryngoscopy and tracheal intubation using a randomization table. The patients arrived in the surgical unit fasted and unpremedicated. They were connected to an electrocardiogram and a peripheral pulse oximeter. End-

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Table 1 Patient characteristics as mean (SD) and range

	LMA	Tracheal intubation
No. of patients	20	20
Age (yr)	7.70 (2.70) 4.1–12.0	7.15 (2.30) 4.3–11.0
Height (cm)	130.3 (17.5) 102–160	125.1 (15.3) 101–150
Weight (kg)	29.48 (11.71) 16.0–55.0	28.43 (13.83) 14.0–70.0
Gender (male/female)	13/7	13/7
ASA class (*n*)		
I	18	19
II	2	1

Table 2 Excitation during induction of anaesthesia and the conditions of the successful attempts to secure the airway

	LMA	Tracheal intubation	*P*-value (Fisher's exact)
Excitation during induction			0.251
None	9	13	
Mild	7	3	
Moderate	1	0	
Severe	3	1	
Conditions of the successful attempts			0.193
Poor	0	2	
Good	4	5	
Excellent	16	10	

tidal sevoflurane concentration and carbon dioxide partial pressure during induction and maintenance of anaesthesia were monitored using a Datex Capnomac airway gas monitor (Datex-Ohmeda, Helsinki, Finland). After loss of the eyelash reflex a catheter was positioned via one of the nostrils in the oropharynx for sampling of the inspired and exhaled gases.[8]

Anaesthesia was induced with sevoflurane in a mixture of air and oxygen (FI_{O_2} 30%) at a concentration of 8% until loss of eyelash reflex, which occurred usually in less than 10 breaths. The patients breathed spontaneously from a Mapleson D circuit with a fresh gas flow of 6–9 litre min^{-1} throughout the study. If the end-tidal carbon dioxide partial pressure increased over 6.0 kPa ventilation was gently manually assisted, targeting an end-tidal carbon dioxide partial pressure of 4.5–6.0 kPa. After loss of the eyelash reflex, anaesthesia was maintained with the predetermined end-tidal concentration of sevoflurane. We used previous data[2 6 7] to give 1.8% end-tidal sevoflurane to the first patient allocated for laryngeal mask insertion and 2.2% the first patient allocated for laryngoscopy and tracheal intubation. The anaesthetist in charge of the patient was not aware of the end-tidal sevoflurane concentration throughout the study. The predetermined end-tidal concentration of sevoflurane was maintained for 10 min to allow adequate time for alveolar and brain sevoflurane partial pressures to equilibrate.[9] An attempt to secure the airway was then performed using either a standard multiple-use LMA or an uncuffed single-use tracheal tube. If the attempt failed (a failure was defined as any visible relevant spontaneous movement such as withdrawal or flexor movement of the arms or legs, frowning of the forehead muscles, coughing or bucking within 1 min of LMA insertion or laryngoscopy and tracheal intubation),[2 6 7] the end-tidal sevoflurane concentration was increased by 0.3% end-tidal and another 10 min was allowed to elapse before the next attempt. If this second attempt failed the end-tidal sevoflurane concentration was increased again by 0.3% end-tidal and another 10 min was allowed to elapse before the third attempt. The difference between the inspired and end-tidal sevoflurane concentration was less than 10% at the time of each attempt to secure the airway.[10] If the third attempt to secure the airway failed no further attempts were made as it was considered unethical to expose the patient to further attempts and the patient was then managed as considered appropriate by the anaesthesiologist in charge of the patient. The study ended at the first successful attempt or after the third unsuccessful attempt to secure the airway. If the attempt to secure the airway succeeded, the assigned end-tidal sevoflurane concentration for the next patient in that group was decreased by 30% of that of the successful attempt. If the third attempt to secure the airway failed, the assigned sevoflurane end-tidal concentration for the next patient in that group was that used at the third failed attempt. The sevoflurane concentration and the result of each attempt of securing the airway were recorded. The conditions of each successful LMA insertion or laryngoscopy and tracheal intubation were recorded as poor, good or excellent. Adverse effects, particularly excitation, during sevoflurane induction and maintenance were also recorded and graded none, mild, moderate or severe.

Statistics

All statistical analyses were performed using the SAS (SAS Institute Inc., Cary, NC, USA) statistical software. Fisher's exact test was used to compare the groups regarding excitation and conditions of the successful attempts to secure the airway. Success of the LMA insertion or laryngoscopy and tracheal intubation was analysed using the logistic regression model to determine those sevoflurane end-tidal concentrations where 50% (EC_{50}) and 95% (EC_{95}) of the attempts were successful.[11] Differences between the groups in EC_{50} and EC_{95} values were evaluated by *t*-tests. Data are presented as mean (SD) except were indicated and a *P* value of less than 0.05 was considered statistically significant.

Results

The patient characteristics of the groups were similar (Table 1). Eleven patients allocated to LMA insertion and four patients allocated to laryngoscopy and tracheal intubation (data of three patients missing) experienced mild to severe excitation during induction (Table 2). No

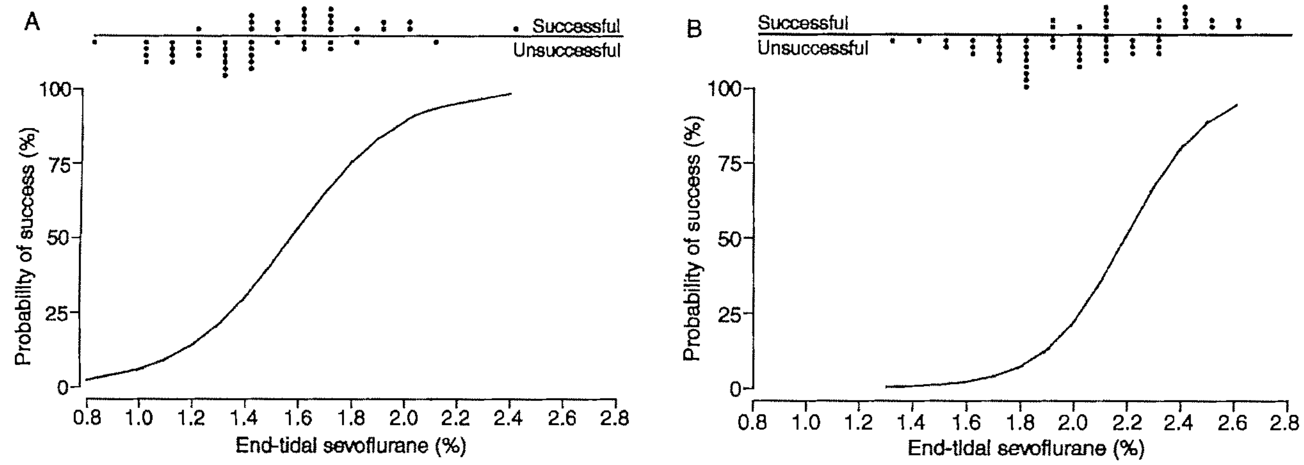

Fig 1 (A) The probability of successful LMA insertion (%) versus end-tidal sevoflurane concentration (%). Each dot represents one attempt. The EC_{50} of sevoflurane for LMA insertion was 1.57 (0.33)% and the EC_{95} was 2.22% end-tidal ($P<0.001$). The slope of the logistic curve is 4.85 (SEM 1.48). (B) The probability of successful laryngoscopy and tracheal intubation (%) versus end-tidal sevoflurane concentration (%). Each dot represents one attempt. The EC_{50} of sevoflurane for laryngoscopy and tracheal intubation insertion was 2.20 (0.31)% and the EC_{95} was 2.62% end-tidal ($P<0.001$). The slope of the logistic curve is 6.56 (SEM 1.84).

other adverse effects were observed during the study. The conditions during the successful attempts were generally good in both groups (Table 2). The EC_{50} and the EC_{95} of sevoflurane were 1.57 (0.33)% and 2.22% end-tidal for LMA insertion and 2.20 (0.31)% and 2.62% end-tidal for laryngoscopy and tracheal intubation, respectively ($P<0.001$ for both variables; Fig. 1).

Discussion

The minimum alveolar concentration (MAC), for example the concentration for achieving a 50% probability of no response to skin incision is the most widely used measure of anaesthetic potency for volatile anaesthetics.[9 10 12] However, it represents only one measure of potency, and other points on the concentration response curve are also of interest. Indeed, the concentration of the volatile anaesthetic that prevents a response to a stimulus in 95% of patients (EC_{95}) is clinically more useful than the EC_{50}. Previous studies on securing the airway under sevoflurane anaesthesia in children have focused on the EC_{50}.[2 6] Therefore, our study was designed to determine both the EC_{50} and the clinically more relevant EC_{95} for LMA insertion and for laryngoscopy and tracheal intubation in children.

We found that (1) sevoflurane in general provided good conditions in unpremedicated children for both LMA insertion and for laryngoscopy and tracheal intubation and (2) both the EC_{50} and the EC_{95} of sevoflurane were significantly less for LMA insertion than for laryngoscopy and tracheal intubation. Our values for the EC_{50} of sevoflurane are slightly less than those presented previously. The EC_{50} of sevoflurane has been reported to be approximately 2.0% end-tidal for LMA insertion[2] and in the range of 2.66–2.83% end-tidal for laryngoscopy and tracheal intubation.[2 6 7] There is one report of an EC_{95} of 3.54% end-tidal of sevoflurane for laryngoscopy and tracheal intubation.[7] These differences may be caused by several methodological differences between these studies and our study. In all previous studies, only one attempt to secure the airway was allowed for each child.[2 6 7] In two of these studies, the up-and-down method was used which only allows EC_{50} values to be measured.[2 6] Our study design, with three attempts at increasing sevoflurane concentrations for each child, increases the number of observations, particularly for unsuccessful attempts. This allowed us to assess both ends of the concentration response curve more closely than if only one attempt was allowed for each child. However, the possible carry-over effect of sevoflurane from the previous step of sevoflurane and attempt cannot be excluded. The 10 min equilibration period that we used for alveolar and brain sevoflurane partial pressures to equilibrate between each attempt should have been sufficient for sevoflurane, which has a blood-gas partition ratio coefficient of approximately 0.65.[7 9 10] We also used a smaller step of sevoflurane changes (0.3% *vs* 0.5% end-tidal) than the other studies.[2 6 7] This may have increased the accuracy in our study when the response to securing the airway was determined. Finally, we utilized the logistic regression model to calculate the EC_{50} and the EC_{95} values, instead of using a more simple method applied in the up-and-down technique. The use of the logistic regression model in the assessment of dose-response curves has recently been evaluated. The accuracy of the parameter estimates has been questioned, particularly when small samples such as the present one are being evaluated.[13] In spite of this criticism the logistic regression model remains the only robust method to estimate both the EC_{50} and the EC_{95} values and it allows comparison of these values with those of previous similar studies.[11 13] These differences in methods probably cause small differences in the EC_{50} and EC_{95} values in our study and those reported previously. However, the results of our study are essentially in the same range as those reported previously.[2 6 7]

We conclude that, the LMA provides a safe and feasible alternative to secure the airway in children with significantly less sevoflurane requirements than needed for laryngoscopy and tracheal intubation. The LMA might be particularly practical for securing the airway in children during procedures that do not require deep levels of anaesthesia or during procedures that are performed under sedation and regional anaesthesia.

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Effect of common airway manoeuvres on upper airway dimensions and clinical signs in anaesthetized, spontaneously breathing children

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Chin lift, jaw thrust and these manoeuvres combined with continuous positive airway pressure (CPAP) can be used to improve the patency of the upper airway during general anaesthesia. We used video endoscopy and measurement of stridor to compare the efficacy of these manoeuvres in 24 children (3–10 yr) with adenotonsillar hyperplasia. A bronchofibrescope was passed via the nose while the children were breathing spontaneously, to identify (i) the shortest transverse distance between the tonsils during inspiration and during expiration and (ii) the distance from the tip of the epiglottis to the posterior pharyngeal wall. Chin lift or jaw thrust lifted the epiglottis and, when combined with CPAP (10 cm H_2O), there was a significant lateral displacement of the tonsils. Both chin lift plus CPAP and jaw thrust plus CPAP reduced stridor significantly compared with the unsupported condition. In conclusion, in spontaneously breathing children with large tonsils, chin lift plus CPAP is recommended, whereas jaw thrust plus CPAP is no better and may cause post-operative discomfort.

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Keywords: anaesthesia, general; airway; surgery, paediatric; anaesthetic techniques, inhalation; anaesthetics volatile, halothane

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Maintenance of the airway is an important aspect of the safe administration of anaesthesia to children. Failure to maintain a patent airway can result in hypoxaemia despite an increase in inspired oxygen fraction. The airway obstruction associated with general anaesthesia is generally attributed to reduced genioglossus activity and consequent posterior displacement of the tongue.[1 2] Any drug that reduces the activity of the pharyngeal muscles can reduce airway patency and thereby increase upper airway resistance.[3] Obstruction can be caused by occlusion of the oropharynx by the tongue[4] or by the epiglottis or soft palate.[5] Although the positions of the head and mandible affect upper airway obstruction, knowledge of the respiratory changes in airway dimensions is still only fragmentary in spontaneously breathing, anaesthetized infants and children. The chin lift manoeuvre is considered to produce a satisfactory upper airway in subjects with a flaccid upper airway.[6] Airway patency is also improved by jaw thrust with continuous positive airway pressure (CPAP) to dilate or splint the upper airway, but little is known about how these techniques work. We studied airway patency using clinical signs and endoscopy to describe the effects of common airway manoeuvres on airway patency in children.

Patients and methods

We studied 24 children (3–10 yr) scheduled for elective adenotonsillectomy. Children with craniofacial abnormalities, deformities of the chest or spine, and myopathies were excluded. The study was approved by the Ethics Committee of the Children's Hospital, Basel, and parents gave written informed consent.

Anaesthesia

Each patient was premedicated with midazolam 0.3 mg kg^{-1} rectally 15 min before anaesthesia. Anaesthesia was induced with ≤3 vol% halothane via a face mask, with oxygen in 50% nitrous oxide from a circle system. Inspired halothane concentration was adjusted to give an end-tidal concentration of 1.0 vol%. Electrocardiogram, pulse oximetry and capnography with breathing frequency were recorded

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(Capnomac Ultima; Datex, Helsinki, Finland). The head position was standardized. The head was slightly extended using a special pillow, to obtain an angle of 110° between the horizontal plane of the operating table and a line connecting the lateral corner of the eye and the tragus of the ear, with neither the occiput of the head nor the shoulders raised above the operating table. We used this angle because a study of adults by Boidin[7] and our own clinical observations in anaesthetized children (unpublished) suggest that this allows maximal widening of the upper airways.

Airway monitoring

We adapted a special airway endoscopy mask[8] and a standardized fixation system (Secutape; TechniMed Ltd, Basel, Switzerland) to tailor the mask to each patient. A bronchofibrescope with an outer diameter of 3.5 mm (Olympus Optical, Volketswil, Switzerland) was inserted through the mask and one nostril into the nasopharynx, leaving the other nostril patent. The tongue and laryngeal structures were examined while the child was breathing spontaneously. The light source for the endoscopy was a xenon lamp (CLV-U40, Olympus Optical Co., Tokyo, Japan). For all measurements, the tip of the fibrescope was kept at the edge of the soft palate to give comparable views at baseline (chin unsupported) and during the subsequent manoeuvres. The manoeuvres were standardized and performed by the same investigator in all children to eliminate inter-investigator variability. A baseline measurement was made with the adapted facemask with the patient's chin unsupported. Then chin lift was done with one hand without making the mandible protrude. The teeth were in light contact and the lips remained open, so the mouth was not completely closed. Then, in addition to chin lift, CPAP of 10 cm H_2O was applied from the circle system to dilate or splint the upper airway. Jaw thrust was applied with both hands, displacing the jaw upwards and anteriorly (Esmarch manoeuvre), which allowed the mouth to remain open. This was done with maximal mandibular protrusion at zero end-expiratory airway pressure and then with CPAP of 10 cm H_2O. After the measurements, the patient's trachea was intubated for subsequent surgery.

Airway patency was assessed clinically as follows: stridor score 1, normal breathing sounds detected by auscultation over the trachea; 2, stridor over the trachea detected by stethoscope; 3, stridor detected without auscultation (audible); 4, no airway sound detectable over the trachea.

Video transformation and image analysis

Records were made for 1 min during each of the different airway manoeuvres on a Super VHS tape (SV-9500 MDP; Sony, Tokyo, Japan). The video sequences were transferred to a Macintosh computer using a frame grabber card (miroMotion DC 20; Miro Computer Products, Braunschweig, Germany). Video information (72 dots per inch, 25 frames per second) was transposed to a PICT format (Adobe Premiere 4.2.1; Adobe Systems Inc., San Jose, CA, USA) and analysed with an image analysis software package (Adobe Photoshop 4.0; Adobe Systems Inc.). The person who performed the image analysis was blinded as to a patient's group. The images with the most narrowed and widened airway dimensions (corresponding to end-inspiration and end-expiration) were identified for the different conditions. The shortest distance between the tonsils (transverse dimension) and the distance between the tip of the epiglottis and the posterior pharyngeal wall (anteroposterior dimension) were measured. These are the most important pharyngeal airway distances during breathing in anaesthetized children.[9]

Statistical analysis

Airway dimensions were expressed as a percentage of distance from baseline, with the chin unsupported. Percentages instead of absolute values were used to reduce the problems of different distance and characteristics between subjects and radial distortion of images caused by the optical characteristics of the fibrescope.[10] The different conditions were compared by repeated-measures analysis of variance. For *post hoc* comparisons, Tukey's test was applied and probability values calculated. Score values were analysed by means of the non-parametric Friedman's test for repeated-measures analysis. Spearman's rank correlation coefficient (r_s) was applied to analyse possible relationships between variables. A P value of <0.05 was considered significant. For all calculations, Statistica/w 4.5 software (StatSoft, Tulsa, OK, USA) was used.

Results

Patient characteristics are presented in Tables 1 and 2. There was no relationship between patient characteristics and subsequent findings.

Both chin lift with CPAP and jaw thrust with CPAP reduced stridor (median score 1.0 (25%–75% interquartile range 0.0) for both) significantly compared with baseline (2.0 (1.5)) and chin lift (2.0 (1.0)) (Figure 1). There was no relationship between inspiratory airway dimensions and stridor scoring, except for the jaw thrust with a CPAP condition (r_s –0.46, $P<0.05$).

All manoeuvres lifted the epiglottis significantly during inspiration (Figure 2). The inspiratory and expiratory

Table 1 Patient characteristics. Data for age, weight and height are mean (SD) (range)

Age (yr)	5.8 (1.8) (3–10)
Body weight (kg)	19.6 (4.7) (12.5–25.8)
Height (cm)	112 (12) (90–126)
History of snoring (*n*)	18/24
History of apnoea (*n*)	8/24

Table 2 Effect of airway manoeuvres on heart rate and breathing frequency. Data are mean (SD) (range). CPAP, continuous positive airway pressure

	Baseline	Chin lift	Chin lift + CPAP	Jaw thrust	Jaw thrust + CPAP
Heart rate, beats min^{-1}	94 (21) (58–150)	92 (19) (62–146)	91 (19) (63–146)	99 (21) (61–146)	98 (23) (64–157)
Breathing frequency, bpm	35 (7) (22–53)	33 (7) (22–49)	36 (8) (22–61)	34 (8) (21–50)	38 (8) (24–62)

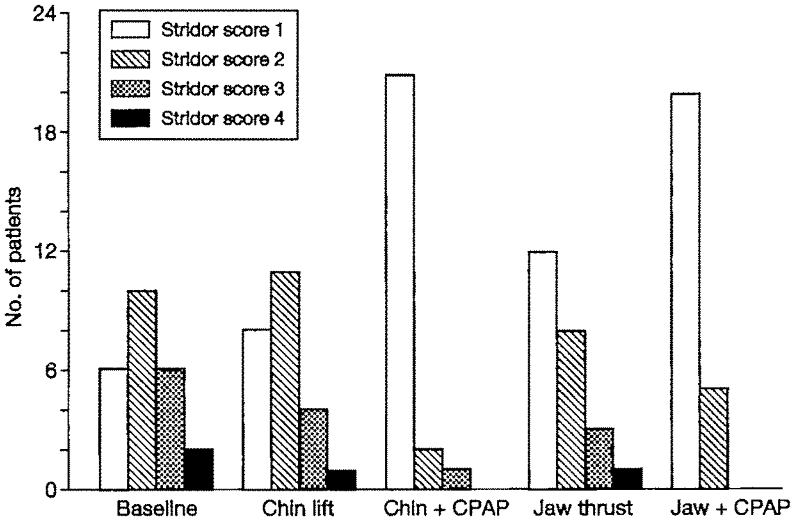

Fig 1 Histogram showing pattern of stridor scoring for airway manoeuvres. Stridor score 1, normal breathing sounds detected by auscultation over the trachea; 2, stridor over the trachea detected by stethoscope; 3, stridor detected without auscultation; 4, no airway sounds detectable over the trachea. CPAP, continuous positive airway pressure.

dimension changes were significantly correlated during all the manoeuvres ($P<0.001$): chin lift: r_s=0.92; chin lift with CPAP: r_s=0.88; jaw thrust: r_s=0.86; jaw thrust with CPAP: r_s=0.92.

Chin lift with CPAP and jaw thrust with CPAP increased the transverse dimension best and were equally effective. Chin lift and jaw thrust manoeuvres without CPAP reduced the transverse distance during inspiration in 10 and six patients, respectively (Figure 3). The inspiratory and expiratory dimension changes were significantly correlated during all the manoeuvres ($P<0.001$): chin lift: r_s=0.74; chin lift with CPAP: r_s=0.88; jaw thrust: r_s=0.81; jaw thrust with CPAP: r_s=0.77.

Discussion

We found that in spontaneously breathing children with large tonsils, chin lift or jaw thrust lifted the epiglottis. When combined with CPAP, the tonsils were moved apart.

Effect of anaesthesia

During anaesthesia, a collapsible segment in the upper airway may narrow or close during inspiration.[11] In a study of thoracoabdominal motion in children, clinically significant upper airway obstruction was found at 2 · MAC (minimal alveolar concentration) sevoflurane.[12] We identified airway collapse during late inspiration, which is similar to reports of collapse during sleep.[13] Severe inspiratory collapse may be associated with a marked decrease in intraluminal pressure.[13] The distal pharynx is 'sucked' in and may even obstruct. The lateral walls of the pharynx have a complex architecture, with a number of muscles that have different biomechanical relationships with each other and with other pharyngeal structures.[14 15] In addition to the depression of the activity of upper airway muscles with halothane,[16] other factors, such as the thickness of the lateral pharyngeal wall, may play a critical role.[15 17] Large tonsils also seem to increase airway collapsibility during inhalational anaesthesia. Our study also supports previous findings that the position of the epiglottis in relation to the posterior pharyngeal wall affects airway patency.[18] However, lateral narrowing and posterior displacement of the epiglottis cannot be assessed clinically, for example by airway sounds.

Effect of chin lift (without protrusion of the mandible)

We found that chin lift did not improve the patency of the airway. Upper airway narrowing during inspiration results from an imbalance between inspiratory muscle activity and the negative intraluminal pressure generated during inspiration. Halothane anaesthesia affects phasic activity of inspiratory muscles in a dose-dependent manner.[16] Both

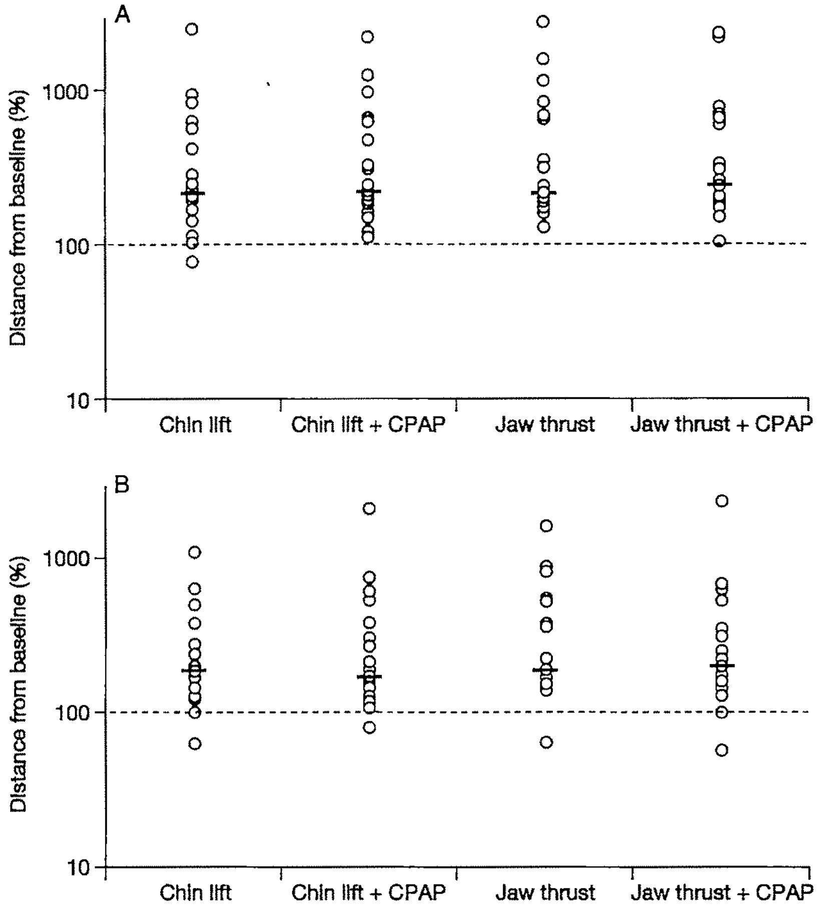

Fig 2 Effect of airway manoeuvre on anteroposterior airway dimensions (distance between the tip of the epiglottis and the posterior pharyngeal wall) during inspiration (A) and expiration (B). Baseline (chin unsupported=100%), dotted line; CPAP, continuous positive airway pressure. Data are skewed and are therefore presented as dot plot and median—on a logarithmic scale. There were no significant differences between the manoeuvres.

anaesthetic agent and the chin-lift manoeuvre affect upper airway muscle tension. The action of negative intraluminal pressure is no longer balanced by the action of the upper airway dilator muscles[19] and severe collapse, with or without complete obstruction, may occur. Lifting the chin could increase pharyngeal compliance so that the tonsils are 'sucked in' without counterbalance from muscle activity. During propofol anaesthesia, chin lift alone could preserve airway patency;[18] however, these children had normal tonsils and this study used magnetic resonance imaging, which did not follow dynamic airway changes.

Effect of jaw thrust (mouth open with maximal mandibular protrusion)

Compared with chin lift, jaw thrust has the advantage that the tension from the tongue and suprahyoid muscles is greater, thus pulling the hyoid ventrally against the root of the tongue and actively widening the pharynx. In addition, the mouth is opened and breathing becomes easier than during chin lift.[20] However, there is no correlation between the degree of the mandibular protrusion and the widening of the pharynx in adults.[21] Mouth opening without mandibular protrusion increases upper airway collapsibility during sleep.[22] We found that jaw thrust manoeuvres, which may cause post-operative discomfort, worsened airway calibre during inspiration, although impairment of airway patency occurred in fewer patients during jaw thrust (six patients) compared with chin lift (10 patients).

Effect of additional CPAP

Continuous positive airway pressure may have several effects, including interactions between changes in chest wall stability, pulmonary mechanics, lung volume and respiratory muscle dynamics.[23 24] Continuous positive airway pressure increases airway volume and airway area within the retropalatal and retroglossal regions and increases lateral dimensions more than anterior–posterior dimensions.[15] In our study, CPAP restored airway patency in children with large tonsils during chin lift and jaw thrust by dilating or splinting the upper airway.

In conclusion, in spontaneously breathing children with adenotonsillar hyperplasia, chin lift plus CPAP is recom-

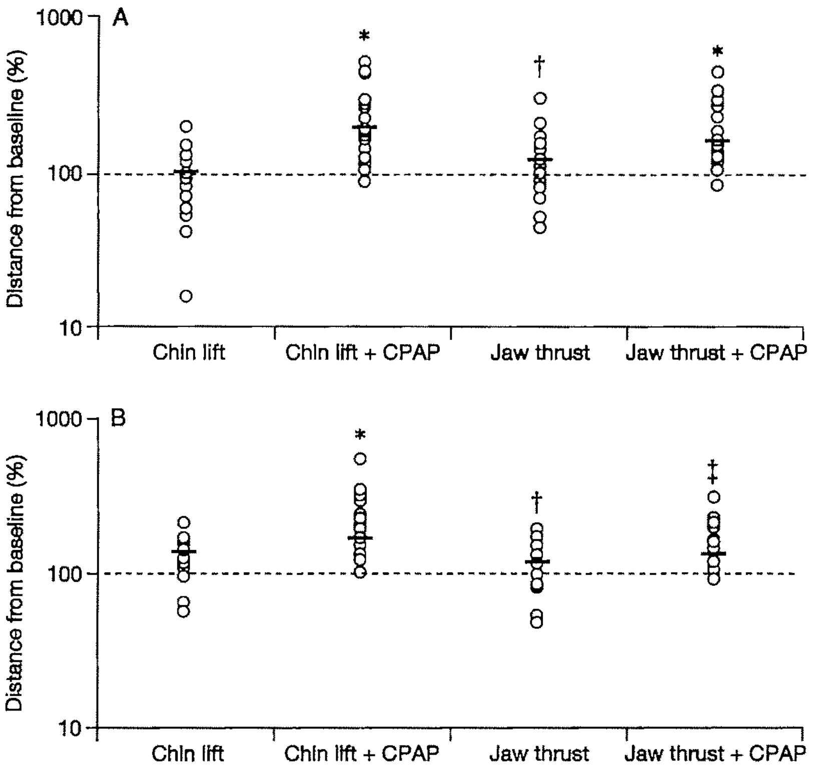

Fig 3 Effect of airway manoeuvre on transverse airway dimensions (the shortest distance between the tonsils) during inspiration (A) and expiration (B). Data are skewed and are therefore presented as dot plot and median—on a logarithmic scale. Baseline (chin unsupported=100%), dotted line; CPAP, continuous positive airway pressure. *Significantly different from chin lift ($P<0.05$); †significantly different from chin lift with CPAP; ‡significantly different from jaw thrust.

mended; jaw thrust plus CPAP is no better and may cause post-operative discomfort. Although little is known about the biomechanics of the upper airway and how the various soft tissues interact mechanically to control the dimensions of the upper airway, the degree of stridor may indicate the efficacy of airway manoeuvres.

Acknowledgements

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Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy

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The pharmacokinetics and time course of action of vecuronium in normal children and children receiving anticonvulsant drugs for prolonged periods were characterized. A bolus dose of vecuronium 0.15 mg kg^{-1} was administered i.v. to 10 non-epileptic children and to 10 children on phenytoin and 10 children on carbamazepine, who were matched for age and weight. Plasma concentrations of vecuronium, 3-OH desacetylvecuronium (the primary metabolite of vecuronium) and α_1-acid glycoprotein (AAG) were determined. Pharmacokinetic variables were derived from plasma samples collected before and after administration of vecuronium. Neuromuscular transmission was monitored by evoked compound electromyography. Recovery of the first twitch of the train-of-four (T_1/T_0) and the recovery index (RI), the time for 25–75% recovery of T_1/T_0, were determined. The elimination half-life of vecuronium was significantly reduced in both anticonvulsant groups compared with control [control 48.2 (SD 40.3), phenytoin 23.5 (13.1), carbamazepine 18.4 (16.6) min, $P<0.05$]. Vecuronium clearance was increased in both anticonvulsant groups [control 9.0 (3.6), phenytoin 15.1 (8.9), carbamazepine 18.8 (13.1) ml kg^{-1} min^{-1}, $0.05<P<0.1$]. Children on chronic anticonvulsant therapy had a significantly shorter RI than control [control 21.8 (11), phenytoin 12.5 (8.3), carbamazepine 10.6 (5.9) min, $P<0.05$]. Concentrations of vecuronium at different degrees of recovery of T_1, volumes of distribution and AAG concentrations were not different between groups. Our data confirm anticonvulsant-induced resistance to vecuronium in children and support a pharmacokinetic component contributing to the resistance.

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Phenytoin and carbamazepine have been the mainstay of anticonvulsant therapy in children for decades.[1] Several clinical studies have demonstrated resistance to the neuromuscular effects of non-depolarizing neuromuscular blocking drugs (NDNMB), particularly NDNMB steroidal relaxants, in patients receiving chronic anticonvulsant drug therapy.[2 3] Phenytoin and carbamazepine are potent inducers of hepatic microsomal enzymes.[4 5] Enhanced hepatic metabolism of NDNMB may account for accelerated inactivation and clearance of these drugs. Recently we reported resistance to rocuronium, a steroidal NDNMB, in children receiving chronic anticonvulsant therapy.[6] Alloul and colleagues demonstrated in adults that a single dose of vecuronium can be metabolized rapidly in patients receiving chronic carbamazepine therapy.[7] These authors concluded that carbamazepine-induced resistance to vecuronium neuromuscular blockade was due to an increase in hepatic clearance. Furthermore, most anticonvulsant drugs currently in use have been shown to increase α_1-acid glycoprotein (AAG) concentrations.[8 9] An increased concentration of AAG can increase the protein binding of cationic drugs and alter their distribution.[10 11] These drug-induced changes in the pharmacological effects of NDNMB could also be confounded by age-related variability. Normal

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children aged 3–10 yr have increased vecuronium requirements and also recover faster than infants, older children and adults.[12 13]

We tested the hypothesis that, in children, long-term phenytoin or carbamazepine therapy alters vecuronium kinetics as a result of hepatic enzyme induction. By measuring plasma vecuronium concentration and its pharmacodynamic effects, we attempted to characterize the pharmacokinetic contribution to the accelerated recovery from vecuronium-induced paralysis occurring in children receiving chronic anticonvulsant therapy.

Table 1 Patient characteristics. Data are mean (SD). No significant differences between groups

	Control	**Phenytoin**	**Carbamazepine**
n	10	10	10
Age (yr)	10.2 (4–14)	11.0 (5–17)	12.1 (4–22)
Males/females	6/4	5/5	64
Weight (kg)	42 (6)	39 (6)	43 (4)

Materials and methods

Subjects

This study was approved by the institutional Human Studies Committee. Children undergoing neurosurgical or orthopaedic procedures were enrolled after informed consent from the patient and/or their parents. Exclusion criteria included patients taking more than one anticonvulsant drug or patients with coexisting hepatic, renal, cardiac or neuromuscular disease. The study patients were assigned to one of three groups (Table 1). The children receiving phenytoin (n=10) or carbamazepine (n=10) had been taking it for more than 1 month. The control group consisted of 10 patients who had no history of epilepsy and were not on chronic medication affecting neurotransmission. Plasma concentrations of phenytoin (5–20 μg ml^{-1}) and carbamazepine (6–10 μg ml^{-1}) were within the therapeutic range immediately before the study for all patients.

Anaesthetic management

Anaesthesia was induced with halothane, nitrous oxide and oxygen or thiopental. Vital signs were monitored in all patients with a sphygmomanometer, electrocardiogram, precordial stethoscope, pulse oximeter and temperature probe. Anaesthesia was maintained with an infusion of fentanyl (3 μg kg^{-1} h^{-1}), and isoflurane (0.2–0.5%) with N_2O and O_2 (2:1 ratio). Oesophageal temperature was maintained at 36.5 (SD 0.5)°C by using a force hot-air blanket and a mattress blanket. After obtaining baseline neuromuscular data over 5 min, vecuronium (0.15 mg kg^{-1}) was administered i.v. to facilitate tracheal intubation. The trachea was intubated and the lungs were ventilated mechanically to maintain end-tidal carbon dioxide at 3.3–4.0 kPa.

Pharmacodynamics of vecuronium

After induction of anaesthesia, the patient's hand was secured to a splint in order to minimize movement artefacts during neuromuscular monitoring. Supramaximal square-wave stimuli were delivered to the ulnar nerve via surface electrodes at 2 Hz for 2 s and repeated every 20 s (train-of-four), and the evoked compound electromyogram (EMG) of the adductor pollicis muscle was recorded (Relaxograph NMT; Datex, Minneapolis, MN, USA). The maximal suppression of the EMG with vecuronium and time to recovery of T_1/T_0 to 0.1, 0.2, 0.25, 0.5, 0.75, 0.8, 0.9 and 1.0 were recorded. The recovery index (RI), calculated as the time taken for T_1/T_0 to recover from 25–75%, was also measured.

Measurement of plasma vecuronium and 3-OH desacetylvecuronium concentrations

Blood samples were collected before and 5, 10, 15, 30, 60, 90, 120 and 240 min after administration of vecuronium. Plasma was separated, frozen immediately at –80°C and analysed later for concentrations of vecuronium and its principal metabolite, 3-OH desacetylvecuronium, using high-performance liquid chromatography with an electrochemical detector.[14] Organon 7465 was used as the internal standard. The lower limit of the assay was 4 ng ml^{-1} and the coefficient of variation was less than 10%.

Plasma vecuronium and 3-OH desacetylvecuronium concentrations were analysed by iterative non-linear least-squares regression techniques on observed concentrations, as described previously (Sigma Plot, Windows, version 4, Jandel, Sunnyvale CA, USA).[15] The slope (beta) of the terminal log-linear phase of each plasma concentration–time curve was determined by linear regression analysis. This slope was used to calculate the apparent elimination $t_{1/2}$. The area under the plasma concentration–time curve from time zero until the last detectable concentration was determined by the linear trapezoidal method. The residual area extrapolated to infinity was calculated as the final concentration divided by beta. These two areas were added to yield the total area under the plasma concentration–time curve. The peak plasma concentration (C_{max}) and the time at which the peak concentration occurred (t_{max}) were used as measures of the rate of appearance of drug in the systemic circulation. Coefficients and exponents from the fitted functions were used to calculate the following kinetic variables: total volume of distribution using the area method (V_d); and total clearance (Cl). The plasma concentration of vecuronium was also plotted against the percent inhibition of T_1/T_0.

Clinical pharmacokinetic–pharmacodynamic modelling

The time-averaged concentration data was fitted to a standard biexponential pharmacokinetic model. Using the models determined for each of the three data sets, the plasma vecuronium concentrations at the times corresponding to each effect level (a given recovery of T_1/T_0) were calculated. The resulting concentration–effect pairs were plotted. A sigmoid pharmacokinetic–pharmacodynamoc model was chosen, and the following equation was used to describe the concentration–effect relationship. E_{max} was assumed to equal 100% twitch depression.

$$E = 100 - \frac{E_{max}C^{A}}{EC_{50}{}^{A} + C^{A}}$$

where E_{max}=maximum effect, EC_{50}=effect compartment concentration at 50% block and A=slope factor of the sigmoid curve.

Plasma AAG concentrations

AAG concentrations were assayed by radial immunodiffusion plates as described previously.[8] Plasma was incubated for 24 h in wells treated with rabbit AAG antiserum in an agarose gel. This solution yielded a precipitin ring. The quantity of AAG in plasma was calculated from the standard curve of AAG 100–2000 μg ml^{-1}. This AAG assay was highly specific and had no cross-reactivity with other proteins, including albumin, haemopexin and α_2-macroglobulin. Correlation between individual AAG concentrations and the corresponding recovery index was analysed.

Statistical analysis

Neuromuscular recovery and the pharmacokinetic data of the three groups were compared by analysis of variance followed by Dunnett's multiple comparisons *post hoc* test. The Pearson product–moment correlation coefficient was calculated to assess the affect of AAG concentrations on the corresponding recovery indices. Data are presented as means (SD). $P<0.05$ was considered significant.

Results

The physical characteristics of the patients in the three groups are listed in Table 1. There were no differences between groups with respect to age, sex or weight.

Pharmacokinetic–pharmacodynamic modelling of vecuronium

The concentration–time data for the parent compound and the metabolite (3-OH desacetylvecuronium) in the three groups are shown in Fig. 1. Volumes of distribution were not different between the three groups. The elimination half-life was significantly shorter for the phenytoin and carbamazepine groups compared with control. There was increased clearance of vecuronium in the phenytoin and carbamazepine groups compared with control, which reached statistical significance in the carbamazepine group (Table 2). As indicated in Fig. 1B, the active metabolite, 3-OH desacetylvecuronium, was detected in all three groups at 1% of the parent drug concentration. The plasma concentration of vecuronium (parent drug only) plotted against recovery of T_1/T_0 to 10, 25, 50, 75 and 100% did not differ between groups (Fig. 2). Sigmoidicity in the pharmacodynamic analysis was evident, and thus a sigmoid pharmacokinetic–pharmacodynamic model was used to describe the concentration–effect relationship. However, examination of the plots revealed no hysteresis, and thus an effect site distinct from the central compartment was not postulated (Fig. 2). There was also no difference in the EC_{50} and slope factor (A) between groups (Table 3).

Vecuronium pharmacodynamics on EMG

Bolus administration of vecuronium 0.15 mg kg^{-1} abolished the twitch response in all patients. The recovery indices from vecuronium-induced block for the children on antiepileptic drugs were significantly faster than those for the control group (Table 3). Recovery T_1/T_0 was also significantly faster in the treatment groups than in the controls (Fig. 3).

Plasma AAG concentrations

The AAG concentrations for the three groups were as follows: control 36.7 (4.6) μg ml^{-1}, phenytoin 44.4 (5.0) μg ml^{-1}, carbamazepine 52.3 (5.4) μg ml^{-1}. These values did not differ significantly. There was no correlation between individual plasma AAG concentration and the corresponding recovery index (Fig. 4).

Discussion

Phenytoin and carbamazepine have direct depressant effects on the neuromuscular junction by a presynaptic and postsynaptic mechanism.[5 16 17] Acute administration of an anticonvulsant drug either suppresses the post-tetanic potentiation of the muscle and endplate potential or leads to a decrease in the release of acetylcholine quanta at the nerve terminal. Thus, in the presence of acute exposure to anticonvulsants, the neuromuscular effects of NDNMBs are enhanced.[18 19] With chronic exposure, however, there is resistance to the neuromuscular effects of NDNMBs. This resistance has been observed with steroidal relaxants (pancuronium, vecuronium, pipecuronium, rocuronium).[7 20 21] Evidence exists for increased elimination of steroidal relaxants in the presence of chronic carbamazepine

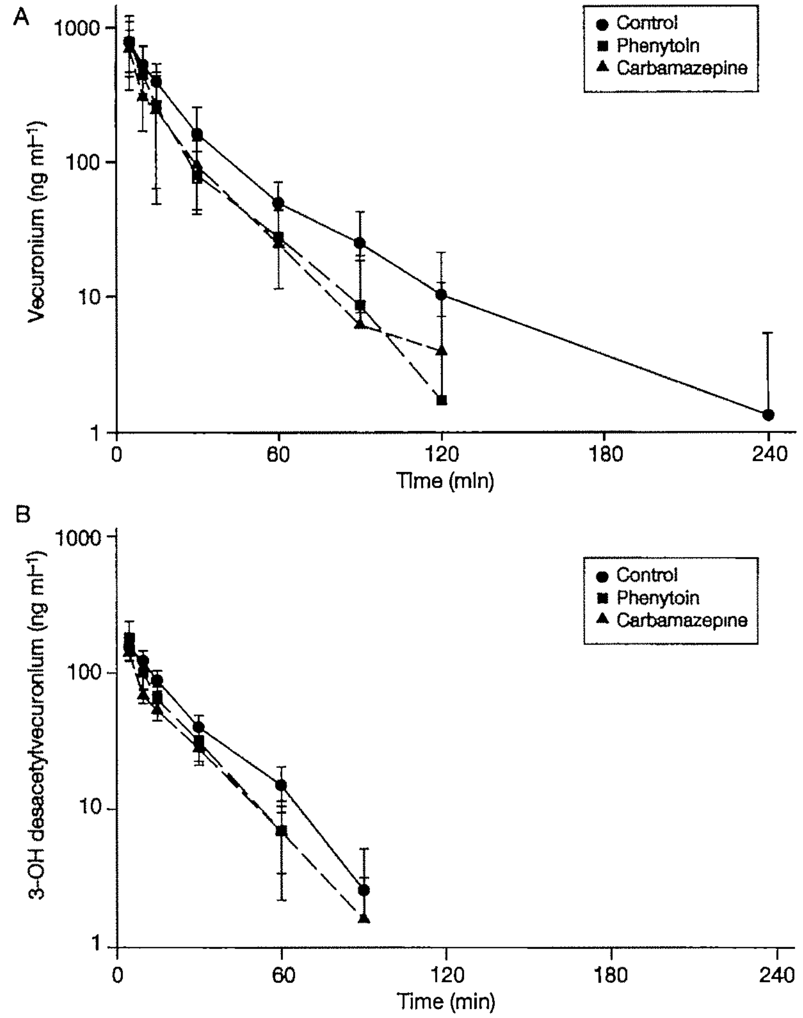

Fig 1 Vecuronium (A) and 3-desacetylvecuronium (B) plasma concentrations are plotted against time (semilogarithmic plot) after a single bolus dose of vecuronium 0.15 mg kg^{-1}. Mean (SD) are plotted for each group. The metabolite 3-desacetylvecuronium could be detected within 5 min of the bolus of vecuronium. There were no significant differences between groups.

or phenytoin therapy.[7,21] This resistance, however, is less common with benzoylisoquinolones (tubocurarine, metocurine, atracurium).[2,22,23] Resistance to the neuromuscular effect of mivacurium in patients taking anticonvulsants has not been observed.[24,25]

Our study in children confirms previous studies in adult patients that chronic administration of either of the anticonvulsants phenytoin and carbamazepine induces resistance to the neuromuscular effects of vecuronium. The resistance was evidenced as a faster recovery of T_1/T_0 to given endpoints and a shorter recovery index relative to controls. Our data give further evidence that changes in the elimination half-life ($t_{\frac{1}{2}}\beta$) are at least partly responsible for the observed resistance to vecuronium. The trend for increased clearance of vecuronium was apparent in both groups and was statistically significant in the carbamazepine group.

Age-related differences in vecuronium pharmacology in normal patients have been reported.[12,13] When compared

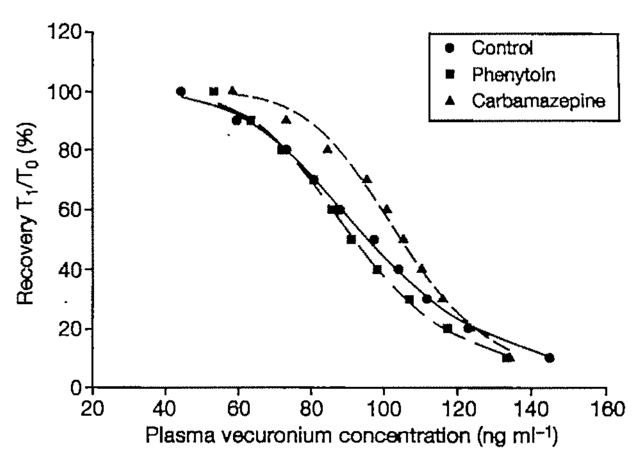

Fig 2 Plasma concentrations of vecuronium are plotted against degree of neuromuscular block. Mean values and the predicted curves are plotted for each group. There were no significant differences between the groups in the hysteresis in the concentration–effect curves.

Table 2 Vecuronium pharmacokinetic parameters. Data are mean (SD). *$P<0.05$ *vs* control

	Control	Phenytoin	Carbamazepine
$t_{1/2}\alpha$ (min)	8.4 (3.7)	6.8 (3.8)	6.1 (0.7)
$t_{1/2}\beta$ (min)	48.2 (40.3)	23.5 (13.1)*	18.4 (16.6)*
V_d (litre kg^{-1})	0.55 (0.52)	0.47 (0.25)	0.32 (0.13)
Cl (ml kg^{-1} min^{-1})	9.0 (3.6)	15.1 (8.9)	18.8 (13.1)*

Table 3 Vecuronium pharmacodynamic parameters. Data are mean (SD). *$P<0.05$ *vs* control. EC_{50}=effect compartment concentration at 50% block; *A*=slope factor of the sigmoid curve

	Control	Phenytoin	Carbamazepine
Onset time (min)	1.40 (0.16)	1.38 (0.11)	1.21 (0.11)
Recovery index (min)	21.8 (11)	12.5 (8.3)*	10.6 (5.9)*
EC_{50} (ng ml^{-1})	95.6 (4.7)	91.1 (4.1)	104.8 (7.6)
A	5.17 (0.95)	6.15 (1.26)	7.83 (2.85)

with infants and adults, young children aged 3–10 yr had a higher ED_{95} for tracheal intubation.[26] Furthermore, they had significantly shorter recovery times than infants and adults.[12,13] The ED_{50} of vecuronium to produce depression of adductor pollicis twitch tension reported by Fisher and Miller was 19.0 μg kg^{-1} for children and 15.0 μg kg^{-1} for adults.[12] These authors concluded that the increased volume of distribution in children mediated the increased requirement for vecuronium. In our study, the average age of the patients was 11 yr and the age distribution was similar between groups. Thus, age-related differences in elimination or distribution kinetics are not the cause of the faster recovery observed in the treatment groups.

The aetiology of the decreased sensitivity to NDNMB after prolonged anticonvulsant therapy may be multifactorial. Phenytoin and carbamazepine are both potent inducers of hepatic microsomal enzymes by induction of cytochrome P-450 isoenzyme III A4, resulting in enhanced elimination of many drugs.[18,27,28] The decreased half-life and the trend for increased clearance in the anticonvulsant-treated group is consistent with the reports of Alloul and colleagues[7] and Szenohradszky and colleagues [21] in adults, where enhanced elimination kinetics of vecuronium or rocuronium was observed in patients on anticonvulsants.

The potential for anticonvulsants to induce qualitative or quantitative changes at the neuromuscular junction, and therefore resistance to NDNMBs, is also present. A known side-effect of anticonvulsants is muscle weakness resulting from a decrease in the spontaneous and evoked quantal release of acetylcholine.[5,18] In addition, these drugs also have effects that simulate the actions of curare-like drugs on the prejunctional membrane nerve terminal.[29,30] Therefore, these anticonvulsant drugs behave prejunctionally like botulinum toxin and postjunctionally like NDNMBs. Thus, chronic exposure to anticonvulsant drugs may induce a 'denervation syndrome' in which the expression of immature receptor isoforms leads to upregulation of acetylcholine receptors. [31] These upregulated acetylcholine receptors can either increase the effective dose or have altered sensitivity to NDNMB because of the expression of immature isoforms of the receptors.[30] Animal and human studies have provided direct and indirect evidence for upregulation of acetylcholine receptors after chronic anticonvulsant therapy.[8,32] Kim and colleagues reported a proliferation of acetylcholine receptors at the muscle membrane after chronic phenytoin therapy in rats.[8] Furthermore, patients on anticonvulsant therapy had increased sensitivity to succinylcholine, consistent with the possibility of upregulated acetylcholine receptors.[32]

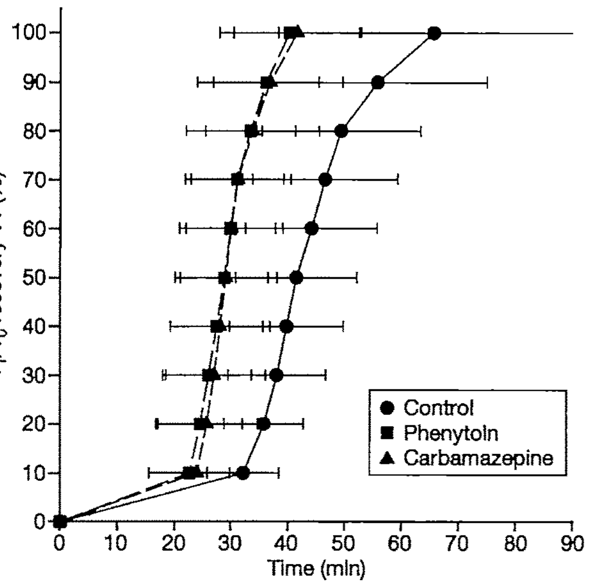

Fig 3 Per cent recovery T_1/T_0 is plotted against time after a single dose of vecuronium 0.15 mg kg^{-1}. Data are mean (SD) for all three groups. Recovery times for the phenytoin and carbamazepine groups were significantly different from control.

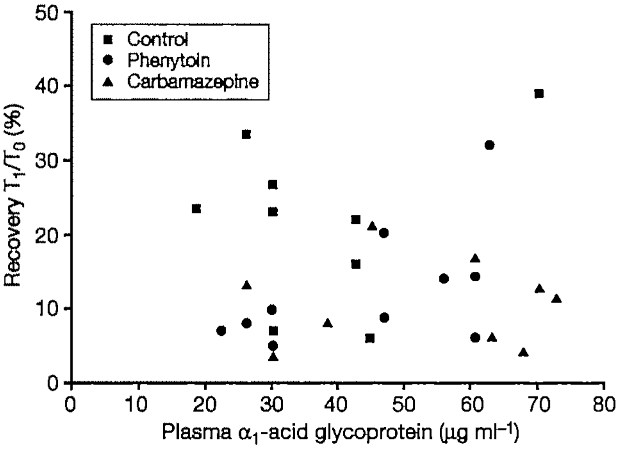

Fig 4 Plot of individual plasma α_1-acid glycoprotein concentrations against recovery T_1/T_0. Pearson product-moment correlation coefficient analysis showed no significant relationship between the two variables.

In our study, plasma concentrations of vecuronium at specific degrees of neuromuscular blockade did not differ significantly between the three groups. At first glance, this finding could be interpreted as a lack of difference between groups in drug–receptor kinetics or target organ sensitivity. This conclusion cannot be reached definitively on the basis of the findings of this study. A major metabolite of vecuronium is 3-OH desacetylvecuronium, which has potent neuromuscular blocking properties that can be additive or synergistic with its parent compound.[33] Thus, it is possible that the concomitant presence of the metabolite in the plasma (and at the target tissues) confounded these observations. However, the plasma concentration of the metabolite was 1% of the parent compound, which would have a negligible effect on neuromuscular blockade.

Another possible cause of the resistance is alterations in plasma protein binding caused by anticonvulsant-induced increases in AAG concentrations.[8–10 34 35] This protein can potentially bind to many cationic drugs, including NDNMBs, and thus reduce their efficacy and alter the unbound concentration. In the rat, long-term phenytoin administration resulted in increased concentrations of AAG and a decrease in the free concentration of metocurine, partially explaining the resistance.[8] In our study, plasma concentrations of AAG in both anticonvulsant groups were not statistically different. The reason for this is unclear. We conclude that increased AAG concentrations did not significantly contribute to the resistance to vecuronium observed in this study. This conclusion is consistent with that of Hans and colleagues, who reported that elevated concentrations of AAG induced by chronic anticonvulsant therapy did not contribute to the rapid recovery from vecuronium blockade.[35]

In summary, this study confirms previous studies in adults that the resistance to vecuronium in children on chronic anticonvulsant therapy is partly related to increased metabolism. Previous studies have indicated altered drug–receptor kinetics as an additional cause of the resistance to NDNMBs. But the contribution of altered pharmacodynamics to the resistance to vecuronium could not be determined in this study. These results do not exclude the additional possibility of changes in target organ sensitivity to account for the resistance.

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Epidural analgesia and arterial reconstructive surgery to the leg: effects on fibrinolysis and platelet degranulation

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It has been suggested that the incidence of early graft occlusion after arterial reconstructive surgery to the leg may be decreased by epidural analgesia. This effect may be mediated by the suppression of the usual cortisol response to surgery, which results in increased circulating plasminogen activator inhibitor-1 with consequent adverse effects on fibrinolysis. To investigate this and other potential mechanisms, 30 patients undergoing arterial reconstructive surgery to the leg were randomized to receive either general anaesthesia or general anaesthesia plus epidural analgesia. Post-operative analgesia was provided by morphine infusion or epidural analgesia, respectively. Blood samples were collected at 0, 2, 4, 6, 12 and 24 h, and 2, 3 and 5 days and analysed for cortisol, plasminogen activator inhibitor-1 antigen, interleukin-6 and beta thromboglobulin. The incidence of graft-related and systemic complications was recorded for 30 days. Only one patient developed early graft occlusion that required embolectomy and eventually amputation. There were no significant changes from control values in either group of patients in circulating cortisol, plasminogen activator inhibitor-1 and beta thrombogobulin (a marker for platelet degranulation). Interleukin-6 values increased significantly in both groups after 4 h and remained elevated until day 3. There were no significant differences between the groups in any variable measured. We conclude that any effect of epidural analgesia on early graft patency is unlikely to be mediated by fibrinolysis or platetlet degranulation.

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Patients undergoing arterial reconstructive surgery to the leg are at high risk of perioperative cardiovascular and respiratory complications, early occlusion of their graft requiring urgent embolectomy, further surgery or amputation of the limb. Studies, which attempted to decrease early morbidity and mortality by the use of regional anaesthesia, concluded that the choice of anaesthetic, provided it was carefully conducted, had no influence on overall morbidity or mortality.[1–3] However, it is possible that anaesthesia may affect the success of the graft. Christopherson and colleagues found that epidural analgesia decreased early graft occlusion from 22 to 4%.[2] This improvement was attributed to enhanced fibrinolysis measured by changes in plasminogen activator inhibitior-1 (PAI-1).[4] The authors postulated that epidural analgesia prevented the usual cortisol response to surgery, and that the cortisol response results in an increase in PAI-1, with adverse effects on fibrinolysis.

If epidural analgesia improves the success of arterial reconstructive grafts, it is important to determine the mechanism(s). There are other potentially beneficial effects of epidural analgesia in addition to the postulated influence on fibrinolysis. For example, platelet aggregation is inhibited,[5] sympathetic block increases leg blood flow,[6] and an i.v. fluid load decreases blood viscosity.[7] Systemic effects of local anaesthetics include decreased plasma viscosity[8] and platelet aggregability,[9] and increased prostacyclin production.[10] Good analgesia after surgery, with the prevention of pain-mediated vasoconstriction, may also be important.

To investigate some of these potential mechanisms we examined the effects of epidural analgesia on changes in serum cortisol, fibrinolysis, platelet degranulation and cytokine release for 5 days after arterial reconstructive surgery to the leg. Circulating cortisol concentrations were

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measured to establish the usual endocrine response to this surgery and its relationship to plasminogen activator inhibitor-1 antigen (PAI-1 ag). Changes in platelet degranulation were assessed by measurement of circulating beta thromboglobulin (βTG). The interleukin-6 (IL-6) response to surgery was determined, not only to indicate the severity of the inflammatory response to surgical trauma, but also because IL-6 initiates acute phase protein synthesis thus increasing several prothrombotic factors.[11]

Methods

With the approval of the Local Research Ethics Committee and after written informed consent, 30 patients were randomized to receive either general anaesthesia (GA) or general anaesthesia plus epidural analgesia (GAE) for arterial reconstructive surgery to the leg. Patients were included in the study if they were scheduled for vascular reconstruction below the inguinal ligament and excluded if there were contraindications to epidural analgesia such as a coagulopathy and local or systemic sepsis.

Pre-operative assessment of the patients included the Goldman risk index[12] the ankle brachial pressure index (ABPI) and the indications for surgery. Patients were randomized, using random number tables, to receive either GA or GAE. All operations started between 08.00 and 11.00 h and routine cardiac medications were continued until 2 h before surgery. Insulin-dependent diabetic patients had an i.v. infusion of glucose and insulin from 06.00 h on the morning of surgery maintaining blood glucose at 5–10 mmol litre^{-1}. The infusion was continued for 24 h after surgery when oral intake and the usual insulin regimen were resumed. Non-insulin-dependent diabetic patients had oral hypoglycaemic drugs stopped 12 h before surgery and were also managed with a glucose-insulin infusion during and after surgery. Patients taking aspirin continued with the drug until hospital admission.

Premedication was not given and, in the anaesthetic room after routine non-invasive monitoring was established, a wide bore, peripheral venous cannula and a radial artery cannula were inserted using local anaesthesia. All patients received an i.v. fluid load of 0.9% sodium chloride solution 10–12 ml kg^{-1} and a sleep dose of thiopentone. Neuromuscular block was established with vecuronium 0.1 mg kg^{-1}, the trachea intubated and anaesthesia maintained with nitrous oxide in 40% oxygen and isoflurane. During surgery bolus doses of vecuronium and fentanyl up to 5 μg kg^{-1} were given, as needed.

Epidural analgesia was established in the GAE group at the L2-3 interspace and a test dose of 0.5% bupivacaine 3 ml was given followed by increments of 0.25% bupivacaine to establish a block to at least T10. Anaesthesia was induced as in the GA group but with a maximum of fentanyl 50 μg. During surgery epidural analgesia was maintained with an infusion of 0.25% bupivacaine 6 ml h^{-1}. In all patients a central venous cannula and urinary catheter were inserted after induction of anaesthesia.

During surgery, 0.9% sodium chloride solution was infused at 5–8 ml kg^{-1} h^{-1} and gelatin solution given to replace blood loss unless the haematocrit was <30% when packed red cells were transfused. Anaesthesia and fluid therapy were adjusted to maintain mean arterial pressure within 20% of pre-induction values and a heart rate of 60–100 beats min^{-1} with optimal filling. All patients received i.v. heparin 5–7000 units during surgery which was undertaken by the same surgical team of experienced consultants. Vein grafts were reversed and grafts were either femoral popliteal or femoral-distal in site. The technical success of the graft was confirmed by an intraoperative arteriogram.

At the end of surgery, neuromuscular block was reversed with neostigmine 2.5 mg and glycopyrronium 0.5 mg, the trachea extubated and the patient transferred to a high dependency area. Oxygen was given postoperatively by facemask to maintain Pa_{O_2} >10 kPa and 0.9% sodium chloride solution infused at 1–2 ml kg^{-1} h^{-1}. Analgesia was provided by an i.v. morphine infusion in the GA group and by the epidural infusion of 0.125% bupivacaine+fentanyl 10 μg ml^{-1} in the GAE group. In addition to routine haemodynamic monitoring, pulses, perfusion and temperature in the operated leg were recorded hourly and pain measured every 4 h. Epidural analgesia or a morphine infusion were continued for at least 18 h after surgery and followed by oral analgesics.

Blood samples were collected before induction of anaesthesia, at 0, 2, 4, 6, 12 and 24 h after the start of surgery and at 08.00 h on days 2, 3 and 5. Samples for the measurement of cortisol and IL-6 were centrifuged and the serum stored at –70°C. Samples for the determination of PAI-1 ag were collected in refrigerated stabilyte tubes (Biopool) containing 1/10 volume strong acid citrate, transferred on ice, centrifuged immediately and the top third of supernatant plasma stored at –70°C. Blood for βTG analysis was collected in tubes containing 1/10 volume anticoagulant (Dipotassium EDTA 5.42 g, theophylline 0.36 g, adenosine 0.267 g, 0.19% saline 100 ml), and immediately double centrifuged to ensure removal of all platelets before storage at –70°C. If venepuncture was necessary to obtain the sample, the first 2–3 ml were discarded.

Serum cortisol concentration was measured by ELISA (Milennia Cortisol EAI), which had a sensitivity of 7.3 nmol litre^{-1}, intra-assay coefficient of variation (CV) of 3.2% and inter-assay CV of 8.0%. IL-6 values were determined with a sandwich ELISA (Quantikine R and D systems) which had a sensitivity of 0.7 pg ml^{-1}, intra-assay CV of 4.3% and inter-assay CV of 6.3%. PAI-1 antigen was measured by ELISA (Biopool TintElize) with a sensitivity of 2 ng ml^{-1} and an inter-assay CV of 2.5% at 40 ng ml^{-1}. βTG was estimated by non-proprietary ELISA in which rabbit antiserum to human βTG was purified with *n*-octanoic acid and used to coat microtitre plates (Maxisorb, Nunc, Denmark). Standards

Table 1 Patient characteristics. Table indicates number of patients except for age, weight, ABPI and Goldman risk score which are shown as mean (range) [SD]

	General anaesthesia	**General anaesthesia plus epidural anaglesia**
M/F	12/3	11/4
Age (yr)	71 (54–87) [8.6]	69 (53–88) [10.2]
Weight (kg)	73 (50–97) [13.0]	68 (45–92) [13.9]
IDDM/NIDDM	3/3	0/3
Never smoked	3	2
Ex-smoker	8	2
Currently smoking	4	11
IHD	5	4
Previous MI	2	3
Hypertension	10	6
ABPI	0.29 (0–0.83) [0.29]	0.33 (0–0.79) [0.29]
Goldman risk score	4.0 (0–12) [3.9]	5.5 (0–12) [4.9]
Previous vascular surgery		
None	6	5
Limb angioplasty	3	4
Peripheral vascular	3	4
Carotid surgery	1	1
Coronary artery graft	2	1
Medication		
Calcium antagonist	5	4
Digoxin	1	3
ACE inhibitors	4	3
Aspirin	5	7
Reason for surgery		
Critical ischaemia	6	7
Claudication	6	5
Rest pain	2	3
Gangrene	1	0
Graft type		
PTFE	10	10
Vein	4	5
No graft	1	0

Table 2 Perioperative management. Values shown are mean (range) [SD]

	General anaesthesia	**General anaesthesia plus epidural analgesia**
Pre-operative		
Haematocrit (%)	39 (31–45) [4.5]	38 (33–48) [4.5]
Base excess	1.0 (–4.8 to 4.3) [2.5]	1.6 (–1.4 to 5.5) [1.9]
Intraoperative		
Preload (ml)	1010 (700–1500) [302]	987 (700–1200) [155]
Duration of surgery (min)	117 (80–260) [49]	117 (80–360) [81]
Blood loss (ml)	934 (200–5600) [1359]	519 (200–1500) [363]
Colloid infused (ml)	1030 (0–3500) [828]	953 (0–4000) [1018]
Blood transfused (ml)	495 (0–1400) [144]	235 (0–1400) [413]
Postoperative		
Haematocrit (%)	32 (29–34) [3.5]	31 (28–34) [2.3]
Base excess	–4.2 (–11.8 to 1.1) [3]	–3.3 (–7.0 to –0.1) [2]
Core temp (°C)	35.7 (33.5–36.7) [0.9]	35.5 (34.5–36.2) [0.5]
Lactate (mmol litre^{-1})	1.0 (0.1-1.7) [0.6]	0.9 (0.2–1.7) [0.5]
ABPI	0.83 (0.43–1.0) [0.2]	0.86 (0.48–1.0) [0.2]

were calibrated against the 1st International Standard (83/501, National Institute for Biological Standards and Controls, Potters Bar, UK). Samples and standards were added to the plates and incubated for 1 h, washed and labelled with tag antibody (diluted biotin antibody/horseradish peroxidase/streptavidin), and incubated for an 1 h. After further washing, enzyme activity was measured by the addition of substrate solution (*o*-phenylenediamine hydrochloride 10 mg and 30% hydrogen peroxide 7 μl in 0.1 M citrate phosphate buffer 15 ml, pH 5.0) and stopped after 10 min with 2 M sulphuric acid. Absorbance was read at 492 nm. Intra-assay CV was 3.7% and inter-assay CV was 4.3%. All assays were undertaken in duplicate.

Patients were assessed until discharge to monitor the outcome of surgery and the incidence of complications. Failure of the arterial graft was defined as a decrease >0.3 in the ABPI, need for anticoagulation, embolectomy, regrafting and amputation. Cardiovascular, respiratory, infectious and renal complications were noted as defined by Christopherson and colleagues.[2]

The sample size of 30 patients was based on the expected effect of epidural analgesia on the cortisol response, and had the power of 80% to detect a standardized difference of 1.0 with a significance level of 0.05. Statistical analysis was undertaken with SPSS version 6.1. The results were analysed with chi-squared test, one-way analysis of variance and two-way analysis of variance for parametric and non-parametric data as appropriate. $P<0.05$ was considered statistically significant.

Results

The details of the patients studied including pre-operative characteristics, previous vascular surgery, current medication, reason for surgery and type of graft were similar in both groups (Table 1). Perioperative management of the patients was not significantly different between the groups, in particular the fluid preload, duration of surgery and intraoperative fluid management (Table 2). Graft-related and systemic complications were uncommon and there were no significant differences between the groups (Table 3). The patient who died had an intra-operative blood loss of 5600 ml and succumbed in the intensive care unit to multiple organ failure on the sixth postoperative day. Four patients returned to theatre within 24 h of surgery, three with bleeding and one for an embolectomy. The latter patient required further embolectomies and finally a below knee amputation.

Changes in circulating variables are shown in Table 4. There were no significant differences between groups in cortisol, IL-6, PAI-1 ag and βTG concentrations. There were no significant changes from pre-induction values in both groups for cortisol, PAI-1 ag and βTG values. However, IL-6 concentrations increased significantly in both groups after 4 h and remained significantly elevated until day 3 ($P<0.05$).

Discussion

No effect of epidural analgesia was found on the circulating variables chosen to represent the hormonal, inflammatory, fibrinolytic and platelet degranulation responses during and after arterial reconstructive surgery to the leg. Furthermore, the only variable to show a significant increase during the study was IL-6. Baseline βTG values were increased (normal range 10–40 ng ml^{-1}), reflecting the enhanced platelet activation found in elderly patients with vascular disease.[13 14] We chose to compare GA with GAE to ensure that any differences observed were the result of regional block. An anaesthetic technique of epidural analgesia and sedation would have introduced other variables, but the benefits of avoiding GA merit investigation.

Perioperative morbidity is common after arterial reconstructive surgery as the patients are usually elderly, often hypertensive and diabetic, most are current or ex-smokers and widespread arterial disease is common.[15] Silent ischaemia and perioperative myocardial infarction occur frequently, with coronary artery disease the major cause of early and late mortality.[16 17] Previous studies failed to show any benefit from regional anaesthesia in decreasing perioperative mortality and morbidity.[1–3] Early graft occlusion is an important cause of morbidity and occurs in 6–10% of patients within 30 days of surgery and results in anticoagulation, embolectomy, or further surgery.[18 19] Christopherson and colleagues found an impressive decrease in early occlusion of the graft in patients receiving epidural analgesia, from 22 to 4%.[2] Our results failed to replicate these findings and early graft occlusion occurred in only one patient who required embolectomy and eventually amputation (Table 3). There are many possible reasons for this difference, for example the mean duration of surgery was <2 h in the present study and >5 h in Christopherson *et al.*,[2] but our low rates of graft occlusion are similar to those reported recently by other groups using GA and regional anaesthesia.[20 21] It is possible, therefore, that this influential study of Christopherson and colleagues is not representative of arterial reconstructive surgery to the leg in other major centres.

The mechanism proposed for the beneficial effects of epidural analgesia on graft patency was an attenuation of the perioperative increase in PAI-1, thus decreasing the inhibition of fibrinolysis. PAI-1 is a serine protease inhibitor produced by endothelial cells, and increased concentrations are associated with thrombosis.[22] Rosenfeld and colleagues only measured PAI-1 activity on three occasions within 72 h of surgery, and found significantly lower values in epidural patients at the end of surgery.[4] The authors suggested that the increase in PAI-1 was secondary to increased cortisol secretion, but circulating values were not measured. A later report of urinary cortisol excretion in a sub-group of 60 patients in this study failed to show an effect of epidural analgesia[23] suggesting that any link between cortisol and PAI-1 was tenuous. The inability of epidural analgesia to alter fibrinolysis was also found in a study of patients undergoing knee arthroplasty.[24]

Table 3 Graft-related and systemic complications

	General anaesthesia	**General anaesthesia plus epidural analgesia**
Reoperation in 24 h for		
Bleeding	1	2
Embolectomy	0	1
Early complications		
Respiratory	1	1
Renal	1	0
Wound infection	0	3
Death	1	0
30-day complications		
Amputation	0	1

Table 4 Changes in mean (SEM) circulating cortisol (nmol $litre^{-1}$), PAI-1 ag (ng ml^{-1}), IL-6 (pg ml^{-1}) and βTG (ng ml^{-1}) concentrations in GA patients and GAE patients. There were no significant differences between the groups. IL-6 concentrations increased significantly in both groups from 4 h to day 3 ($P<0.05$)

		Time									
		Pre	**0**	**2 h**	**4 h**	**6 h**	**12 h**	**24 h**	**Day 2**	**Day 3**	**Day 5**
Cortisol (nmol $litre^{-1}$)	GA	605	469	342	604	652	628	699	580	659	624
		(65)	(75)	(57)	(72)	(60)	(57)	(66)	(80)	(44)	(65)
	GAE	567	480	296	524	591	729	701	541	559	702
		(76)	(64)	(57)	(79)	(80)	(111)	(109)	(93)	(72)	(71)
PAI-1 ag (ng ml^{-1})	GA	44	35	38	50	47	47	42	45	51	45
		(5)	(4)	(4)	(5)	(4)	(5)	(4)	(4)	(2)	(5)
	GAE	40	31	38	50	47	47	42	45	51	45
		(5)	(3)	(4)	(5)	(4)	(5)	(4)	(4)	(2)	(5)
IL-6 (pg ml^{-1})	GA	11	10	12	72	96	89	102	64	38	14
		(2)	(2)	(2)	(20)	(20)	(14)	(17)	(10)	(11)	(4)
	GAE	9	8	12	40	72	113	121	66	35	19
		(3)	(3)	(3)	(6)	(12)	(33)	(20)	(8)	(9)	(4)
βTG (ng ml^{-1})	GA	125	133	215	235	213	253	136	155	159	155
		(16)	(18)	(56)	(58)	(54)	(44)	(16)	(22)	(27)	(27)
	GAE	114	90	109	175	152	233	123	201	144	161
		(13)	(10)	(19)	(13)	(14)	(57)	(20)	(43)	(21)	(26)

The pattern of circulating cortisol response to arterial reconstructive surgery to the leg has been poorly defined.[5] We observed no difference between the GA and GAE groups for up to 5 days, but also no change from baseline values indicating that, with appropriate anaesthesia and postoperative analgesia, peripheral arterial surgery causes little stimulation of the hypothalamic-pituitary adrenal axis. We cannot exclude the possibility that the low incidence of early graft occlusion in this study was related to the absence of a cortisol response.

Surgery evoked a rapid increase in IL-6 that was sustained until day 3 and was unaffected by epidural analgesia. Ischaemia and reperfusion injury also stimulate IL-6 production and this may have contributed to the response, which was greater than that found after routine abdominal surgery.[25] IL-6 induces acute phase protein synthesis in the liver.[11] Some of these proteins, fibrinogen and C reactive protein (CRP), are prothrombotic, and the binding of fibrinogen to platelets is one of the early events in arterial thrombosis. Plasma CRP concentrations correlate with the presence and severity of peripheral arterial atherosclerosis,[26] and this acute phase reactant also stimulates an increase in tissue factor which initiates the extrinsic pathway of coagulation.[27] Many of these prothrombotic factors are produced in response to tissue damage and so will be unaffected by neural block. The importance of surgical trauma in the development of the prothrombotic state is shown by the failure of stress hormone infusions to mimic postoperative hypercoagulability.[28]

Patients with vascular disease have platelets with increased aggregability because of factors such as age, hypertension, and hyperlipidaemia.[13 14] A further increase in platelet activation during surgery results from exposure to damaged endothelium and thrombin formation, but catecholamines, angiotensin and IL-6 may also be implicated. Epidural analgesia might decrease platelet activation by effects on leg blood flow, a reduction in catecholamine secretion and even a direct effect of bupivacaine itself.[9] Thromboelastograph studies in major vascular surgery showed a decrease in platelet-fibrinogen interactions with epidural analgesia.[29] These early stages of platelet activation are reversible, whereas degranulation occurs later and is irreversible. We used βTG to assess platelet degranulation and found no effect of epidural analgesia. These results may have been influenced by the marked activation that was already present in the patients before surgery, so that any beneficial effects of epidural analgesia were not apparent. Although patients continued to take aspirin until the day before surgery, this was unlikely to have affected the βTG data.[30]

We conclude that the supplementation of GA with epidural analgesia in patients undergoing arterial reconstructive surgery to the leg is not associated with changes in cortisol, PAI-1, IL-6 and βTG responses.

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Intrathecal sufentanil and morphine for post-thoracotomy pain relief†

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In this double-blind randomized study we compared a group of 15 patients undergoing thoracotomy who received a spinal injection of sufentanil 20 μg combined with morphine (200 μg) after induction of general anaesthesia with a control group of the same size. Post-operative pain was rated on a visual analogue scale (VAS) and a verbal rating scale at rest and with a VAS on coughing. In the recovery room, patients received titrated i.v. morphine until the VAS score was <30, and were followed by patient-controlled analgesia (PCA) for 72 h. The intrathecal sufentanil and morphine group had a lower intra-operative requirement for i.v. sufentanil and needed less i.v. morphine for titration in the recovery room. I.v. PCA morphine consumption and pain scores were lower in the active group than in the control group during the first 24 h. There were no differences after this time. Spirometric data (peak expiratory flow, forced vital capacity and forced expiratory volume in 1 s) were similar in the two groups. We conclude that the combination of intrathecal sufentanil and morphine produces analgesia of rapid onset and with a duration of 24 h.

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Post-thoracotomy pain is one of the most severe types of post-operative pain, and its management is a considerable challenge. Several analgesic techniques, including intercostal, paravertebral, interpleural and epidural blocks with local anaesthetics and opioids, have been used to provide pain relief after thoracotomy.[1] All these techniques have limitations, including short duration of action with intercostal nerve blocks, lack of efficacy with interpleural block and side-effects such as respiratory depression, urinary retention, and nausea and vomiting with epidural opioid analgesia. Although the administration of epidural local anaesthetics and opioids after thoracic surgery is considered the cornerstone of analgesic management, experience with intrathecal administration of opioids is limited.[1]

The intrathecal administration of morphine in post-operative patients was first reported in 1979.[2] Although in the following years this technique was shown to provide effective analgesia of long duration in the post-operative period, its use has been restricted compared with epidural analgesia, because of the alleged higher incidence of side-effects with intrathecal opioids.[3] Nevertheless, intrathecal opioid administration has been investigated more recently in the context of major surgery, especially cardiac.[4–10]

The onset and duration of action of intrathecal and epidural opioids depend on their lipid solubility.[11] Intrathecal morphine has a long duration of action but a slow onset of action. On the contrary, lipid-soluble opioids such as fentanyl and sufentanil have a rapid onset but shorter duration of action. Combining epidural morphine and sufentanil may produce analgesia of rapid onset and long duration.[12 13] Intrathecal administration of both drugs may produce a similar profile and therefore we performed a study of this technique in patients after thoracic surgery.

Patients and methods

Thirty ASA I–III patients with lung cancer scheduled for lung resection by a posterolateral thoracotomy were included in this double-blind, randomized study, after written informed consent had been obtained and ethics committee approval had been given. Patients more than 80 yr or less than 18 yr old were excluded, as well as those with disorders of haemostasis or thoracic spine abnormalities.

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Patients were allocated to a control group or a group given intrathecal morphine and sufentanil (SM group). Randomization was performed on the morning of surgery. In both groups, premedication consisted of flunitrazepam 1 mg. Anaesthesia was induced with propofol 2.5 mg kg^{-1} and sufentanil 0.5 µg kg^{-1}. Tracheal intubation was facilitated by atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with isoflurane (end-tidal concentration 0.8–1.5%). Any increase in arterial pressure (systolic arterial pressure >130 mm Hg or >150% of the preinduction value) and tachycardia (>120 min^{-1} or >150% of the preinduction value) led to the administration of sufentanil 0.5 µg kg^{-1}. A pulsed warm-air device (Bair Hugger®, Augustine Medical Inc., Eden Prairie, MN, USA) was applied to the lower body to maintain body temperature during surgery. Indicators for extubation were recovery from anaesthesia, spontaneous breathing (end-tidal carbon dioxide ≤42 mm Hg), a stable haemodynamic condition and normothermia.

In the SM group, intrathecal administration of opioids was performed before surgical incision through a 24 G Sprotte needle inserted in the L3–4 or L4–5 vertebral interspace, in the lateral position. Patients received 4 ml of a solution containing sufentanil 20 µg and morphine 200 µg. In the control group, patients had the skin prepared with antiseptic and covered with an adhesive dressing in an identical manner to the intrathecal group.

When patients complained of pain in the recovery room, they received a titrated dose of morphine (2 mg bolus at 5 min intervals) until the visual analogue scale (VAS) score was <30. They were then given access to an i.v. patient-controlled analgesia (PCA) pump (APM®, Abbott, Rungis, France) delivering 1 mg morphine bolus doses with a 7 min lockout interval (maximum dose 30 mg 4-hourly). Morphine was diluted to 1 mg ml^{-1} in a solution also containing droperidol 5 mg in 50 ml. PCA was maintained for 72 h. After 3 days, analgesia was maintained by subcutaneous administration of morphine.

Post-operative pain was evaluated by an anaesthetist blinded to treatment groups, using a VAS graded from 0 (no pain) to 100 (worst pain imaginable) and a verbal rating scale (VRS) (0=no pain; 1=mild; 2=moderate; 3=severe; 4=unbearable). Measurements were performed at rest and on coughing with the VAS, and at rest only with the VRS, 1, 2, 4, 6, 12, 18, 24, 36, 48 and 72 h after arrival in the recovery room.

Side-effects, including respiratory depression (respiratory rate <8 b.p.m.), sedation (not rousable except by persisting verbal or tactile stimulation), urinary retention (requiring transient bladder catheterization), nausea, vomiting and pruritus, were recorded at the same intervals.

Spirometry was performed for the determination of forced expiratory volume in 1 s (FEV$_1$), peak expiratory flow rate (PEFR) and forced vital capacity (FVC), before surgery and at 6, 24, 48 and 72 h after surgery.

The main goal of the study was to demonstrate a 50% difference in i.v. morphine consumption between the two groups. Assuming that mean (SD) morphine consumption would be about 50 (25) mg per 24 h, we calculated that a sample of 20 patients would be enough to detect such a difference with a type I error of 0.05 and a type II error of 0.10. Statistical analysis was by unpaired Student's *t*-test for comparison of patient characteristics, duration of surgery, i.v. sufentanil and morphine doses and extubation delay. Two-way analysis of variance and the Scheffé F-test were used to compare VAS scores. The Mann–Witney rank sum test was used to analyse morphine consumption and VRS scores. $P<0.05$ was considered significant.

Results

Patient characteristics, duration of surgery and extubation delay were similar in the two groups (Table 1). The mean dose of i.v. sufentanil during surgery was significantly greater in the control group (Table 2). The mean titrated dose of i.v. morphine in the recovery room was also significantly greater in the control group. The time to the first administration of PCA was similar in the two groups. Over the first 24 post-operative hours, i.v. morphine consumption was significantly lower in the SM group but it was similar in the two groups between 24 and 72 h (Table 2 and Fig. 1). Cumulative i.v. morphine consumption was greater in the control group from 8 to 24 h (Fig. 1).

In the recovery room, most of the patients were unable to cough at 15 and 30 min. VAS scores at rest and on coughing were significantly higher in the control group from 1 to 24 h (Figs 2 and 3). VRS scores were also significantly higher from 1 to 24 h (Table 3). Values of PEFR, FEV$_1$ and FVC were not significantly different between the groups but post-

Table 1 Patient characteristics, duration of surgery and extubation delay. Data are mean (SD). No significant differences

	Control group	SM group
Sex (M/F)	9/6	12/3
Age (yr)	63 (31–85)	56 (42–71)
Weight (kg)	67 (19)	72 (11)
Height (cm)	169 (10)	174 (7)
Duration of surgery (min)	89 (31)	96 (31)
Extubation delay (min)	28 (17)	24 (22)

Table 2 Mean (SD) i.v. opioid consumption.*$P<0.05$

	Control group	SM group
Intraoperative i.v. sufentanil (µg)	34 (11)*	24 (10)
I.v. morphine in recovery (mg)	7.6 (3.6)*	3.4 (4.3)
Time to first PCA i.v. bolus (min)	118 (27)	150 (98)
0–24 h PCA morphine consumption (mg)	36 (15)*	18 (15)
24–72 h PCA morphine consumption (mg)	31 (23)	27 (27)

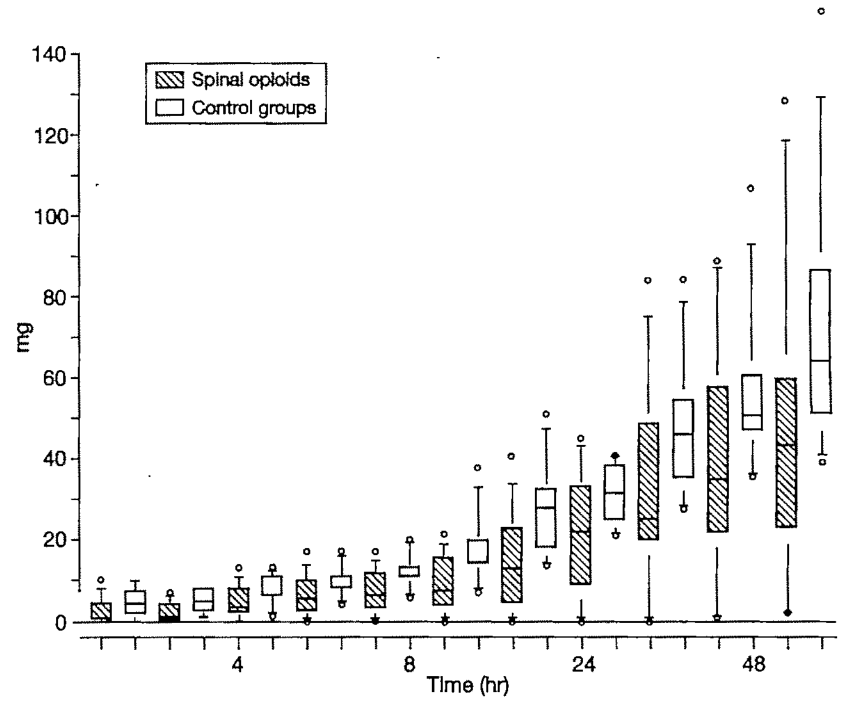

Fig 1 Distribution of cumulative morphine i.v. dose. Values are presented as box plots (25th–75th percentiles) with bars showing the median and the 10th and 90th percentiles and open circles the extremes. At each time interval, the first box represents patients receiving intrathecal sufentanil + morphine (opioid group) and the second box the control group. Values for the control group are significantly greater than those for the opioid (sufentanil + morphine) group from 8 to 24 h ($P<0.05$).

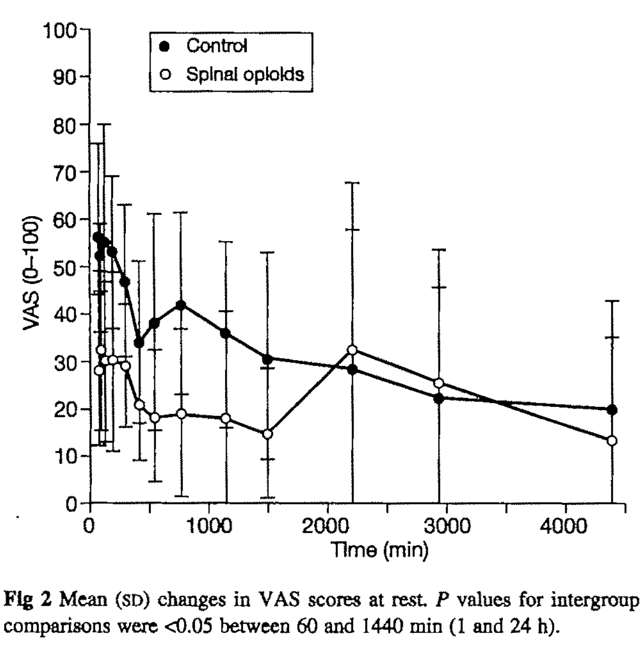

Fig 2 Mean (SD) changes in VAS scores at rest. *P* values for intergroup comparisons were <0.05 between 60 and 1440 min (1 and 24 h).

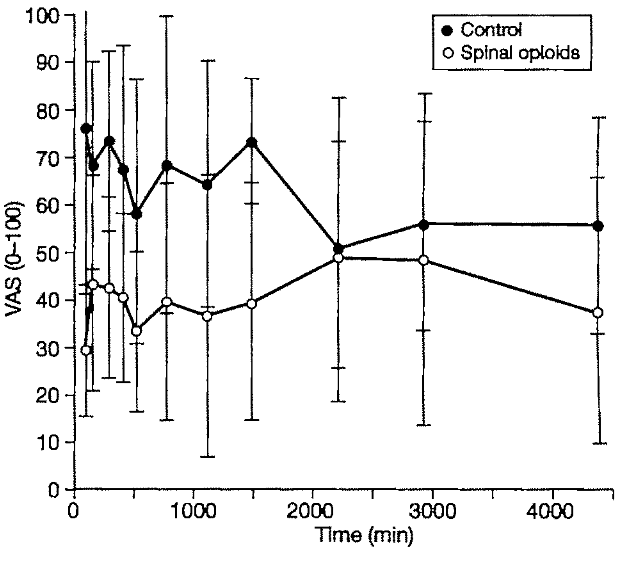

Fig 3 Mean (SD) changes in VAS scores on coughing. *P* values for intergroup comparisons were <0.05 between 60 and 1440 min (1 and 24 h).

operative values decreased significantly in both groups compared with pre-operative values (Fig. 4).

Six patients in the SM group and four in the control group suffered urinary retention (not significant), no patient received naloxone and three patients in each group complained of nausea and vomiting.

Discussion

This study demonstrated that intrathecal administration of a combination of sufentanil and morphine after thoracotomy resulted in a 50% reduction in the i.v. morphine requirement over the first 24 post-operative hours, while VAS and VRS scores at rest and on coughing were also lower during the same period. After 24 h, i.v. morphine consumption and pain scores were similar in the two groups.

Only three previous double-blind, randomized studies have assessed the use of intrathecal opioids for post-thoracotomy analgesia, despite the simplicity of the technique.[4 5 7] One of these[5] demonstrated the advantages of a combined intercostal block; the others demonstrated that VAS pain scores and i.v. morphine requirements were less in patients receiving either intrathecal morphine[4] or fentanyl.[7] Most of the studies concerning the administration of intrathecal opioids in thoracic or cardiac surgery focused on the first 24 post-operative hours and evaluated pain at rest.[4 5 7 10 14 15] A decrease in rescue i.v. morphine is reported consistently over this period. Chaney and colleagues, who extended the study period to 48 h, found that morphine consumption was reduced only during the first 24 h.[9] In only one study were VAS scores at rest lower over a 30-h period in a treated group that received intrathecal morphine 500 μg.[16]

Table 3 Verbal rating scores at rest. Values are median (extremes).*$P<0.05$

Time	Control group	SM group
15 min	2 (1–3)	2 (0–3)
30 min	2 (0–3)	2 (0–3)
1 h	2 (1–3)	1 (0–3)
2 h	2 (1–3)	2 (0–3)
4 h	2 (1–3)*	1 (0–2)
6 h	2 (1–3)*	1 (0–2)
8 h	2 (0–2)*	1 (0–2)
12 h	2 (0–3)*	0 (0–2)
18 h	1 (0–2)*	0 (0–2)
24 h	1 (1–3)*	0 (0–2)
36 h	1 (0–2)	1 (0–3)
48 h	1 (0–2)	1 (0–3)
72 h	0 (0–3)	0 (0–2)

Morphine was administered at the lumbar level and might achieve effective analgesic CSF concentrations at the thoracic level only after significant cephalad movement of the lumbar CSF. Thus intrathecal morphine might require several hours to produce adequate pain control. To decrease the delay in the action of morphine, we combined it with sufentanil. Although we did not compare the SM group with a group of patients receiving only morphine, the comparison with the control group demonstrates that the combination of morphine and sufentanil is immediately effective in the post-operative period. Indeed, patients in the treated group required less i.v. morphine in recovery despite the greater dose of i.v. sufentanil administered during surgery. Previous data supporting this finding have shown the superiority of intrathecal over the i.v. and epidural routes of sufentanil administration.[17] However, the rapid clearance of sufentanil from the CSF[18] does not guarantee analgesia of long duration, which is better ensured by intrathecal morphine.

The duration of action of the combination of intrathecal morphine and sufentanil was, nevertheless, limited to 24 h. A larger dose of morphine may increase duration but would increase the incidence of side-effects, especially respiratory depression.

Pain at rest was well controlled in patients in the group receiving spinal opioids. On the contrary, some patients in this group and most of the patients in the i.v. morphine (control) group experienced severe pain on coughing during the first 24 h. Despite clear recommendations, only a minority of other studies have measured dynamic pain after thoracic surgery. Perttunen and colleagues reported pain intensity on coughing similar to the present results in patients treated by epidural, paravertebral and intercostal

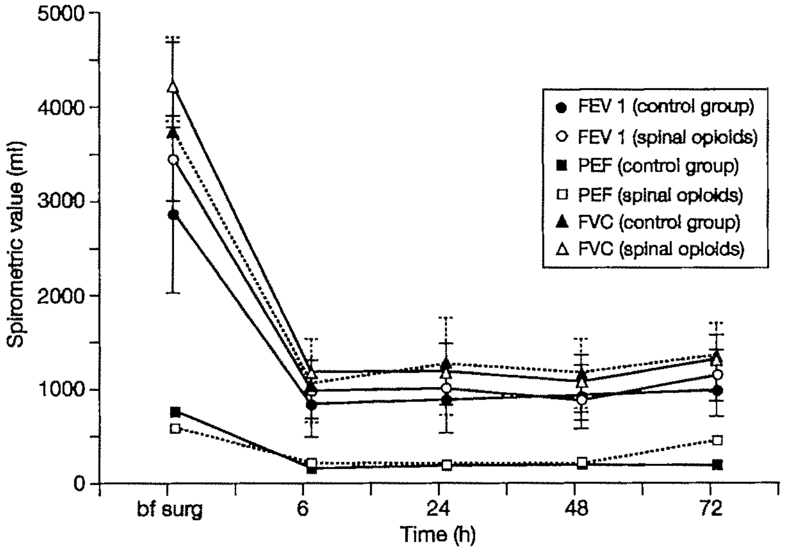

Fig 4 Mean (SD) changes in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV 1) and peak expiratory flow (PEF). Values are not significantly different between the groups. Post-operative values are significantly lower than pre-operative values ($P<0.05$).

nerve blocks,[19] and Guinard and colleagues also described high VAS scores on coughing in patients given i.v. or lumbar or thoracic epidural fentanyl.[20] From these results, it can be concluded that even analgesic techniques considered as being very effective may fail to give complete pain control after thoracic surgery.

Supplementary i.v. morphine was still required in the SM group, indicating that intrathecal opioid administration did not give complete analgesia. Therefore, we consider intrathecal administration to be the core of a multimodal analgesic approach, including parenteral administration of other analgesic agents—an approach recommended by others.[21]

Intrathecal morphine and sufentanil did not delay extubation in the present study. This is at variance with studies concerning coronary artery bypass grafting (CABG).[8] [9] In one study, the authors administered a large dose of morphine (4 mg) but patients received controlled ventilation for more than 12 h.[8] In the other study, the same authors reported that intrathecal morphine 10 $\mu g\ kg^{-1}$ delayed tracheal extubation significantly.[9] This dose was higher than that given in the present study, and the CABG patients also received large i.v. doses of fentanyl during surgery. Shroff and colleagues administered intrathecal morphine 10 $\mu g\ kg^{-1}$ combined with intrathecal fentanyl 25 μg, but they gave i.v. opioid on demand, during CABG.[10] They demonstrated that extubation occurred earlier in the intrathecal group than in the control group. After intrathecal administration of sufentanil 50 μg and morphine 500 μg, 'early' extubation was also possible[6] but, after CABG surgery, whatever the dose of opioid administered, extubation never occurred before several hours of controlled ventilation, making any comparison with thoracic surgery for lung resection rather difficult.

This study confirms the lack of effect of intrathecal opioids on spirometric variables indicative of post-operative pulmonary function, despite better control of post-operative pain.[22] Occasionally, others have demonstrated a marginal correction in the post-operative decrease in respiratory performance.[7] [14] Data from most studies are in agreement with those of the present study, even if it can be demonstrated that effective post-operative analgesia decreases post-operative pulmonary morbidity.[22] Urinary retention was the most worrisome complication in our study, confirming the reports of others.[23]

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Spinal anaesthesia with ropivacaine 5 mg ml^{-1} in glucose 10 mg ml^{-1} or 50 mg ml^{-1}

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Forty patients undergoing spinal anaesthesia for a variety of surgical procedures were randomly allocated to receive 3 ml of ropivacaine 5 mg ml^{-1} in glucose 10 mg ml^{-1} or 50 mg ml^{-1}. Onset of sensory block to T10 was significantly faster (P=0.03) with the glucose 50 mg ml^{-1} solution (median 5 min, range 2–20 min) than with the 10 mg ml^{-1} solution (median 10 min, range 2–25 min). Maximum extent of cephalad spread was virtually the same in both groups (10 mg ml^{-1} median T6/7, range T3–T10; 50 mg ml^{-1} median T6, range T3–T10) with similar times to regression beyond S2 (10 mg ml^{-1} median 210 min, range 150–330 min; 50 mg ml^{-1} median 210 min, range 150–330 min). Complete motor block was produced in the majority of patients (10 mg ml^{-1} 90%; 50 mg ml^{-1} 85%) and the time to complete regression was the same in both groups (median 120 min, range 90–210 min). A block adequate for the projected surgery was achieved in all patients.

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Ropivacaine, a recently introduced amino-amide local anaesthetic agent similar to bupivacaine in chemical structure, has been little studied for intrathecal use. Early evaluation of the drug included two studies of glucose-free solutions performed primarily to allay concern regarding the safety of ropivacaine should accidental intrathecal injection occur during epidural block.[1 2] Sensory block of variable extent and intermediate duration was produced. Currently, ropivacaine is not licensed for intrathecal use, but one clinical study of the plain solution has compared ropivacaine unfavourably to bupivacaine,[3] as did a small study of glucose containing solutions in volunteers.[4] The present study was designed to evaluate the clinical efficacy of hyperbaric solutions containing glucose in two different concentrations.

Methods

Forty patients gave written informed consent for the study that was approved by the local research ethics committee. Patients of ASA grade I–II scheduled to undergo lower abdominal, perineal or lower limb surgery under spinal anaesthesia were recruited and randomized to receive 3 ml ropivacaine 5 mg ml^{-1} with glucose 10 or 50 mg ml^{-1}. Premedication consisted of oral temazepam 10–20 mg.

On arrival in the anaesthetic room, continuous monitoring with ECG, non-invasive arterial pressure and pulse oximetry was commenced and a suitable vein cannulated. No fluid was administered and the patient was placed in the left lateral position for lumbar puncture, which was performed using a midline approach at the 2nd or 3rd lumbar inter-space. A 25 swg Whitacre needle (Vygon, UK) was inserted with the distal port facing laterally and 3 ml of ropivacaine 5 mg ml^{-1} in glucose 10 or 50 mg ml^{-1} was injected over 10–15 s. The study solutions were prepared aseptically immediately before injection by an anaesthetist, who was not one of the investigators, using appropriate volumes of ropivacaine 10 mg ml^{-1}, glucose 100 mg ml^{-1} and sodium chloride 9 mg ml^{-1} (Table 1). The patient was placed supine immediately after injection.

A blinded investigator who did not know which solution had been injected observed the developing block. The extent of sensory block (analgesia to pinprick with a 27 swg short-bevel dental needle), degree of lower limb motor block (modified Bromage scale: 0=full movement; 1=inability to raise extended leg, can bend knee; 2=inability to bend knee, can flex ankle; 3=no movement), arterial pressure and heart rate were recorded at 2, 5, 10, 15, 20, 25 and 30 min, and at 30 min intervals thereafter until complete regression of the block. The caudad limit of sensory block assessment was

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Table 1 Constituents of 0.5% ropivacaine solutions (prepared to 10 ml, 3 ml administered). Densities of solutions at 37°C (mean (SD) n=3 for each solution) measured with DE50 density meter (Mettler-Toledo Laboratories, UK)

Final glucose concentration	Ropivacaine 10 mg ml^{-1} (ml)	Glucose 100 mg ml^{-1} (ml)	Sodium chloride 9 mg ml^{-1} (ml)	Density (g ml^{-1})
10 mg ml^{-1}	5	1	4	1.00273 (0.00019)
50 mg ml^{-1}	5	5	0	1.01531 (0.00002)

restricted to S2 and, where there was a difference in height of block between left and right, the mean of the two was recorded. After 30 min, patients were transferred to theatre for surgery and intra-operative sedation was provided with a target controlled propofol infusion in the dose range 0.5–2.0 µg ml^{-1} (titrated to maintain verbal contact). Hypotension, defined as a decrease of >30% from baseline systolic blood pressure, was treated with i.v. ephedrine 3 mg. Fluids were only administered to replace intra-operative losses and bladder catheterization was performed only if surgically indicated. Patients were visited at 24 h and telephoned at 3–7 days.

The sample size was chosen to show a difference in extent of sensory block of three dermatomes between the groups, based on an α risk of 0.05 and a β risk of 0.20 using data from a previous study of intrathecal ropivacaine.[1] Data are presented as median (range), mean (SD), or frequencies as appropriate. Patient characteristics and the duration of surgery were compared using the two-tailed two-sample *t*-test except for sex (chi-squared test). Block characteristics were compared using the two-tailed Mann-Whitney *U*-test or Fisher's exact test (number of patients with complete motor block). No correction was applied for multiple two-way testing. Statistical advice was that there is no appropriate correction factor available for dealing with sets of data, which, like these, are not strictly independent. In all categories $P<0.05$ was considered statistically significant. Data were analysed using Arcus Quickstat version 1.0 (Research Solutions Ltd, UK).

Results

The groups were comparable with regard to age, sex, height, weight and ASA status (Table 2).

The onset of pinprick analgesia at T10 was more rapid (P=0.03) with the greater concentration of glucose. Median block height was slightly higher throughout in that group (Fig. 1), but the difference was only statistically significant at 90 min (P=0.02).

Degree of motor block was similar in both groups (10 mg ml^{-1} glucose: grade 3 n=18, grade 2 n=2; 50 mg ml^{-1} glucose: grade 3 n=17, grade 2 n=3), and its total duration was the same (Table 3). Complete regression of motor block had occurred at 4 h, and of sensory block at 6 h, in all patients. Cardiovascular changes were minimal and there were no statistical differences between the groups.

Table 2 Patient characteristics and types of surgery in two groups of 20 patients undergoing spinal anaesthesia with ropivacaine 0.5% in glucose 10 mg ml^{-1} or 50 mg ml^{-1}. Data are mean (SD) or frequencies

	Glucose 10 mg ml^{-1}	Glucose 50 mg ml^{-1}
Patient characteristics		
Number of patients	20	20
Female/Male	11/9	16/4
ASA status (I/II)	12/8	11/9
Age (yr)	52 (27–75)	58 (22–88)
Weight (kg)	74 (14)	73 (12)
Height (cm)	168 (9)	166 (10)
Type of surgery		
Lower limb	11	7
Perineal	5	12
Inguinal hernia	3	1
Urology	1	0

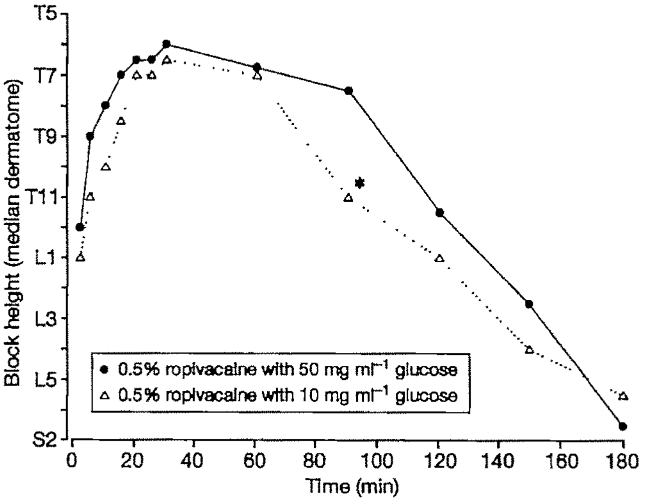

Fig 1 Profile of sensory block in two groups of 20 patients after intrathecal injection of 3 ml ropivacaine 5 mg ml^{-1} with 10 mg ml^{-1} or 50 mg ml^{-1} glucose. *$P<0.05$ between the groups. (60 min: glucose 10 mg ml^{-1} n=12, glucose 50 mg ml^{-1} n=8; 90 min: glucose 10 mg ml^{-1} n=16, glucose 50 mg ml^{-1} n=16.)

The block was suitable for surgery in all patients. Fifteen patients in the glucose 10 mg ml^{-1} group and 12 in the glucose 50 mg ml^{-1} group requested intra-operative sedation. Three patients in each group developed mild localized tenderness at the site of lumbar puncture at 24 h, but there were no neurological symptoms and no patient developed a post dural puncture headache. Hypotension, as defined above, required treatment with a single dose of ephedrine 3 mg in seven patients (10 mg ml^{-1} group, n=4; 50 mg ml^{-1}

Table 3 Characteristics of neural block and frequency of adverse events in two groups of 20 patients undergoing spinal anaesthesia with ropivacaine 0.5% in glucose 10 mg ml^{-1} or 50 mg ml^{-1}. Data are median (range) or number (%); NS=not significant

	Glucose 10 mg ml^{-1}	Glucose 50 mg ml^{-1}	*P*
Sensory block			
Onset at T10 (min)	10 (2–25)	5 (2–20)	0.03
Maximum cephalad spread (dermatome)	T6–7 (T3–T10)	T6 (T3–T10)	NS
Time to maximum cephalad spread (min)	25 (10–30)	20 (10–30)	NS
Block height at 90 min (dermatome)	T11 (T5–L5)	T7 (T6–L3)	0.02
Duration at T10 (min)	108 (35–175)	115 (70–178)	NS
Total duration (min)	210 (150–330)	210 (150–300)	NS
Motor block			
Grade 3 block *n* (%)	18 (90%)	17 (85%)	NS
Time to maximum degree (min)	10 (2–30)	10 (2–30)	NS
Total duration (min)	120 (90–210)	120 (90–210)	NS
Adverse events			
Hypotension	4 (20%)	3 (15%)	NS
Mild back tenderness	3 (15%)	3 (15%)	NS
Transient neurological symptoms	0	0	NS

group, *n*=3), but repeated dosing was not necessary. All patients not requiring catheterization for surgical indications (10 mg ml^{-1} group, *n*=14; 50 mg ml^{-1}group, *n*=10), passed urine normally within 8 h.

Discussion

This study has shown that glucose containing solutions of ropivacaine, hyperbaric relative to CSF,[5] can produce predictable and reliable spinal anaesthesia for a wide range of surgical procedures. This is in contrast to the results of the two early clinical studies of intrathecal ropivacaine, which described blocks that varied widely in extent and were frequently inadequate for surgery.[1] [2] However, those studies used glucose-free solutions. Comparison of individual patient maximum block heights from the current study with those from a group that received the same dose of ropivacaine in one of those earlier studies (with an otherwise almost identical protocol) clearly shows the influence of adding glucose (Fig. 2). The major effect is to reduce the proportion of very limited blocks without producing significantly more extensive blocks, especially at the lower glucose concentration. Similar general findings on the effects of adding glucose have been noted in previous studies of both tetracaine[6] and bupivacaine.[7–10]

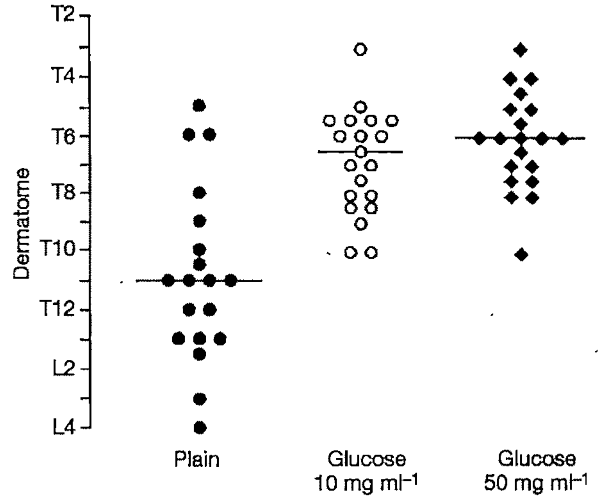

Fig 2 Upper levels of sensory block in individual patients. Horizontal bars represent the medians. Data for plain 0.5% ropivacaine reproduced from van Kleef and colleagues (with permission). All patients received 15 mg ropivacaine in 3 ml.

The results of the current study are also in contrast with the general conclusions of the two more recent studies of intrathecal ropivacaine, both of which questioned its suitability for spinal anaesthesia in comparison with bupivacaine.[3] [4] Gautier and colleagues used plain glucose-free preparations, but in larger volumes of less concentrated solutions that are normally used in clinical practice.[3] When equal doses of ropivacaine and bupivacaine were compared, the onset and extent of sensory block was similar, but the duration of that sensory block and the degree of motor block produced were both less with ropivacaine. These findings, particularly the shorter duration of action, led the authors to claim that ropivacaine is less potent than bupivacaine and that it offers no significant advantage, even though the patients who received ropivacaine passed urine and mobilized more rapidly than those who received bupivacaine.

McDonald and colleagues compared hyperbaric preparations of the two drugs in volunteer subjects not undergoing surgery.[4] Their solutions were also less concentrated than are normally used clinically, as were the total doses injected. Equal doses of ropivacaine and bupivacaine produced sensory blocks of similar onset and extent, but there was less motor block, which regressed faster, with ropivacaine. Again, primarily on the basis of the shorter duration of action, and despite equivalence in the onset and extent of sensory block, the authors concluded that ropivacaine is less potent than bupivacaine. This study also found a higher incidence of backache after ropivacaine and concluded that the incidence of side effects was higher even though the difference was not statistically significant. Although it did not involve any comparison with bupivacaine, our study does not support the implication that ropivacaine is not suitable for spinal anaesthesia.

The features (rate of onset, total spread and rate of offset) of the block produced by the intrathecal injection of any solution are the result of an interaction between the individual patient's characteristics and three completely separate components of the solution, for example: the pharmacological properties of the drug used; the amount (volume, concentration and their product, dose) injected and the physical properties (primarily density relative to CSF) of the solution in which it is administered.

This is because there are two processes involved in the onset of a spinal anaesthetic. First, the solution must spread physically through the CSF. This depends primarily on the properties of the solution, and is independent of the drug's properties. These, along with the dose, will influence the second process, diffusion into (and subsequently out of) the nerve roots.

The factors that influence intrathecal spread have been the subject of a great deal of clinical investigation and this work has been reviewed.[11 12] It is essential that the effects of the different components listed above are identified and recognized because each will impact on the clinical features (rate of onset, total extent, quality/degree and duration) of a spinal block. Thus, when comparisons are made between drugs, the results cannot be assessed properly unless all of the information about the solutions is presented. In addition to drug concentration and the volume injected, data on solution density must be available, especially when non-standard preparations are used. Both Gautier and colleagues, and McDonald and colleagues, used unusually dilute solutions and failed to give details of physical characteristics.[3 4] Even when such information is available, the impact of the various factors on clinical effect must be clearly analysed and understood.

In addition to being a preliminary examination of the features of spinal anaesthesia with ropivacaine, this study formed part of an ongoing programme of work evaluating the factors that influence intrathecal drug spread. This is the primary reason that two different concentrations of glucose were compared. Apart from a slightly slower rate of onset, ropivacaine in glucose 10 mg ml^{-1} produced blocks that were much the same as glucose 50 mg ml^{-1}, replicating a previous finding with tetracaine.[6] Slightly lower glucose concentrations than 10 mg ml^{-1} are needed to produce intrathecal spread that is definitively less widespread.[7 10] Of wider interest is that this study has confirmed the benefit of adding glucose to solutions for intrathecal injection, a finding that has been made repeatedly since the first description of spinal anaesthesia, particularly with the advent of each new drug for this indication.[13]

In conclusion, the addition of glucose to clinically relevant concentrations of ropivacaine can provide reliable spinal anaesthesia of intermediate duration. Further comparative work with bupivacaine is required using clinical effect as a measure of outcome, and not duration of action as a measure of potency, to define the role of this drug for spinal anaesthesia.

Acknowledgements

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Rate of injection through Whitacre needles affects distribution of spinal anaesthesia

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A prospective, randomized, double-blind study was performed to investigate whether altering the rate of injection of local anaesthetic through a Whitacre needle had any effect on the spinal block achieved. Twenty patients scheduled for elective urological surgery under spinal anaesthesia received an injection of 3 ml of 0.5% plain bupivacaine either by hand (fast) over 10 s (18 ml min^{-1}) or by infusion pump (slow) over 3 min (1 ml min^{-1}). All patients were in the sitting position both during insertion of the spinal needle and for 3 min after the start of spinal injection, and they then changed to the supine position. The slow injection group achieved peak sensory block earlier, after a median interval of 20 (95% confidence interval 12.5–30) min *vs* 30 (22.5–45) min ($P<0.05$) for the fast group. The level of peak sensory block was similar: T3.5 (T2–T4.5) *vs* T4 (T1.5–T6.5). The time to lowest mean arterial pressure occurred earlier in the slow group, at 10 (8 to 18) *vs* 20 (15–31) min ($P<0.05$). Duration of the motor block was shorter in the slow group: 180 (152–242) *vs* 270 (225–300). We conclude that a slow spinal injection of plain bupivacaine results in a block of more rapid onset and recovery.

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There are many factors that effect the distribution of local anaesthetics within the intrathecal space.[1] Factors that the anaesthetist has some control over include the physical characteristics of the injectate and the technique of injection.

The recent reintroduction of side-port atraumatic spinal needles has changed the practice of spinal anaesthesia. These needles have a side opening, which can effect the distribution of local anaesthetic agents.[2 3] Also, the flow patterns of fluids injected through these needles have different properties when compared with the conventional Quincke type. *In vitro* work has suggested that flow patterns become turbulent from Whitacre needles at injection rates that are much faster and more clinically relevant than those obtained with Quincke needles of the same gauge.[4 5]

A prospective, randomized, double-blind study was performed to investigate whether altering the rate of injection of the local anaesthetic through a Whitacre needle had any effect on the characteristics of spinal block achieved.

Methods

Twenty patients scheduled for elective transurethral prostate or bladder surgery under spinal anaesthesia were recruited. Patients were aged 18–80 yr, ASA I–III and had no neurological deficits or contraindications to spinal anaesthesia. The study was approved by the hospital Ethics Committee and all patients gave informed consent.

Patients were premedicated 1–2 h before surgery with temazepam 0.3 mg kg^{-1} to the nearest 5 mg. On arrival in the anaesthetic room, non-invasive blood pressure, pulse oximetry and ECG monitoring were applied and an i.v. infusion of Ringer lactate solution (10 ml kg^{-1}) was administered over 15–20 min. Patients were randomized (sealed envelope) by computer-generated random list (Kwikstat 3.01; TexaSoft, Cedar Hill, Texas, USA) to receive either the fast (18 ml min^{-1}) or slow (1 ml min^{-1}) injection rate of spinal anaesthesia.

Lumbar puncture was performed in the midline at the L2,3 interspace under sterile conditions with the patient in the sitting position using a Becton Dickinson Whitacre 25G spinal needle with the orifice pointing cephalad. Once cerebrospinal fluid (CSF) had been identified, 3 ml of 0.5% plain bupivacaine was injected either by hand over a 10 s period (fast) or via a constant infusion pump over 3 min (slow). Patients in the fast group remained seated for a total of 3 min before being gently positioned supine, so that both groups experienced the same duration of positional effects. Oxygen was administered via a face mask at 5 litre min^{-1}

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and sedation with midazolam 1–2 mg increments was given as clinically appropriate. Ephedrine was given if required in 3–6 mg increments to maintain mean arterial blood pressure within 20% of baseline, and i.v. fluids were given to replace estimated surgical blood loss and aid restoration of blood pressure.

Blood pressure, height of sensory block using temperature sensation with ethyl chloride spray and motor block (modified Bromage 4-point scale) were recorded by a blinded investigator at frequent intervals (0, 5, 10, 15, 20, 30, 45, 60, 90, 120 min and hourly thereafter) until complete recovery. Blood pressure was measured every 2.5 min for the duration of the surgery. The dose of ephedrine and i.v. fluid administration was recorded.

Results were analysed by the Student's *t*, χ^2 and Mann–Whitney test as appropriate (Minitab 10.5 for Windows 95). A *P* value of <0.05 was regarded as significant. As there were no previous data on which to base a power calculation, this was considered to be a pilot study and so an empirical number of 20 patients was chosen.

Table 1 Patient characteristics expressed as mean (SD) or ratio. No significant differences

	Fast (*n*=9)	Slow (*n*=11)
Age (yr)	74 (67–81)	74 (66–81)
Height (cm)	165 (12)	165 (8)
Weight (kg)	71 (17)	72 (10)
Sex (M/F)	7/2	11/0
Surgical time (min)	34 (10)	37 (12)

Table 2 Median (95% CI) times in minutes for onset and recovery of sensory and motor blocks. *Significant at $P<0.05$ by Mann–Whitney test

	Fast (*n*=9)	Slow (*n*=11)
Level of peak sensory block	T4 (T1.5–T6.5)	T3.5 (T2–T4.5)
Onset of peak sensory block	30 (22.5–45)	20 (12.5–30)*
Full recovery of sensory block	300 (240–330)	240 (240–270)*
Onset of complete motor block	10 (9–13)	15 (8–29)
Full recovery of motor block	270 (225–300)	180 (152–242)*

Results

All patients had successful spinal anaesthesia and no one was withdrawn from the study. Patient characteristics were similar in the two groups (Table 1).

The level of peak sensory block was similar for the slow and fast groups: median T3.5 (95% confidence interval (CI) T2–T4.5) and T4 (T1.5–T6.5) respectively (Table 2). However, the time to achieve peak sensory block was quicker for the slow injection group: 20 (12.5–30) *vs* 30 (22.5–45) min ($P<0.05$). The onset of sensory block is also shown in Fig. 1. The sensory profile was very similar from 15 min onwards and recovery was identical up to 180 min.

The intensity of the motor block was similar in the two groups (Table 2). Motor block was of shorter duration in the slow group: 180 (152–242) min *vs* 270 (225–300) min for the fast group ($P<0.05$).

The mean arterial blood pressure fell in the slow and fast groups by a similar degree (27 and 20% respectively) (Table 3). However, this occurred nearly twice as rapidly in the slow group (median (95% CI) 10 min (8–18) *vs* 20 (15–31); $P<0.05$). The volume of i.v. fluid infused was similar for the two groups, but the slow group required more

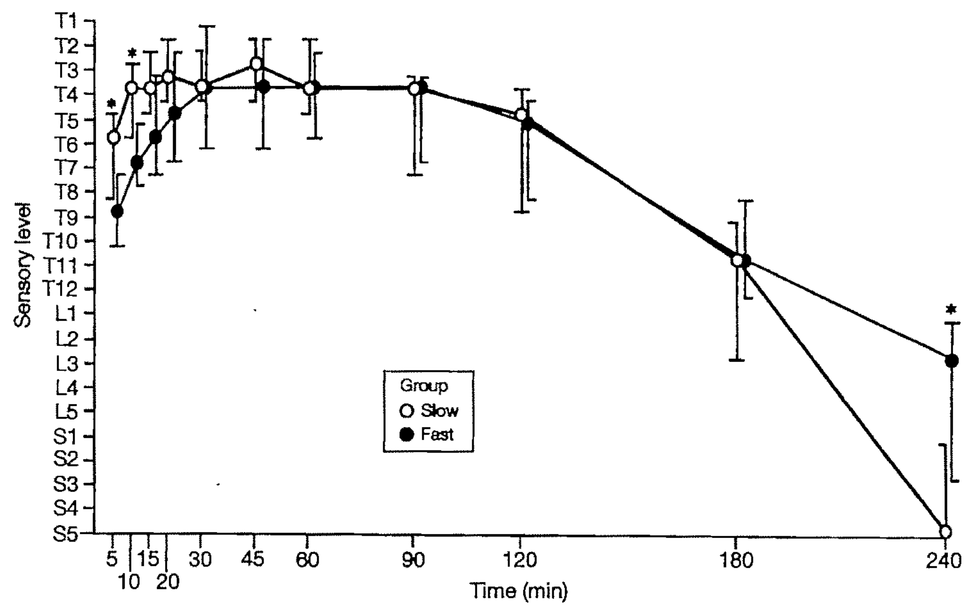

Fig 1 Onset of median (95% CI) sensory level (loss of temperature sensation) after administration of 0.5% bupivacaine 3 ml injected at the speed of 1 ml min^{-1} (slow) or 18 ml min^{-1} (fast). *Significant at $P<0.05$ by Mann–Whitney test.

Table 3 Intra-operative parameters expressed as mean (SD) or median (95% CI). *Significant at $P<0.05$ by Mann–Whitney test. MAP=mean arterial pressure

	Fast (n=9)	Slow (n=11)
Baseline MAP (mm Hg)	101 (14)	94 (8)
Lowest MAP (mm Hg)	81 (17)	69 (11)
Time to lowest MAP (min)	20 (15–31)	10 (8–18)*
Ephedrine (mg)	0 (0–4.5)	7.5 (3–21)*
Intravenous Ringer lactate (ml)	1195 (390)	1410 (700)

ephedrine to maintain the blood pressure (median dose (95% CI) 7.5 mg (3–21) *vs* 0 mg (0 to 4.5); $P<0.05$).

Discussion

The effect of altering the rate of injection of plain local anaesthetics has been investigated previously using Quincke needles.[6–10] The results have been mixed; studies that did demonstrate a higher spread when using the slower rate of injection[6 7] used a much slower injection rate (1 ml min^{-1}) than studies that did not (3 ml min^{-1}).[8–10] *In vitro* work suggests that turbulent flow at the orifice of a 27G Quincke needle starts to occur at very low rates (e.g. 0.25 ml min^{-1}).[5] Such a slow injection rate would be so tedious and difficult to perform that its clinical use would be unlikely. However, the flow pattern from a Whitacre needle of the same gauge becomes turbulent at an injection rate of 2 ml min^{-1}.[4] This injection rate has been used in the clinical management of patients in a couple of studies.[11 12]

In an *in vitro* model, a slow injection was shown to produce a greater spread of local anaesthetic than a faster turbulent flow.[13] With a slow injection, the injectate tended to adhere to and travel further along any surface it contacted in its original direction before the momentum ran out. Conversely, a fast injection produced a turbulent pattern that whirled back from the surface, causing the distribution to be less directional and more mixed and diluted. A mathematical model produced matching results.[14]

Similarly, in our study, a slow injection (1 ml min^{-1}) of 0.5% plain bupivacaine through a 25G Whitacre spinal needle with the patient sitting up and the orifice pointing cephalad produced initially a greater spread of local anaesthetic in the cephalic direction. The local anaesthetic agent was presumably delivered cephalad more quickly and remained concentrated in the posterior compartment of the CSF, where the sensory nerve roots are. This resulted in a more rapid onset of peak sensory block. Plain 0.5% bupivacaine is slightly hypobaric at body temperature and so it will 'float' in the CSF.[15] The fact that the peak sensory block levels were similar in the two groups implies that equal amounts of drug eventually reached the same cephalad level in the posterior CSF compartment. All the patients remained sitting upright for the same period of time and were then positioned supine, so there were no differing gravitational effects. The bupivacaine would have floated upwards along the cephalad border of the thoracic kyphosis (while the patient was supine) to a higher level until diluted enough with the CSF to become thoroughly mixed and no longer affected by gravity. The clinical height of the sensory block then depends on there being the minimal concentration of local anaesthetic required to block a sensory spinal root.[16]

The time for return of normal sensory function in the slow injection group (Table 2) is probably an artefact as the recovery profile of the sensory block was identical for both groups until 180 min. The statistical significance of the measurement at 240 min is almost certainly a chance effect. It is not possible to explain how a sensory block of similar height produced by the same agent could wear off more quickly in one group than in the other.

The onset time of peak sympathetic block was inferred from the time to achieve the lowest mean arterial pressure. The anaesthetist involved (MGS) attempted to maintain the mean arterial pressure within 20% of the baseline level by the early use of fluids and ephedrine. The reduction of blood pressure was more rapid in the slow group. Patients in the slow group required more ephedrine; this probably reflects the fact that the patients had less time to compensate for the haemodynamic changes. The reason for the more rapid sympathetic block is unknown. The sympathetic efferents that maintain vasoconstriction accompany the anterior motor roots, and the onset of motor block was if anything slightly delayed in the slow group. However, sympathetic afferent fibres accompany the dorsal sensory roots, and blockade of these might effect the activity in the sympathetic efferent fibres.

The motor block tended to develop more slowly (though not significantly so) and wore off significantly faster in the slow injection group. This aspect would be a useful clinical advantage in the shorter or daycase type procedure. This may be because, with more cephalic distribution, there was less drug reaching the lower lumbar and sacral motor nerve roots.

There are many studies in the literature concerning slow injection rates through spinal catheters after the appearance of the cauda equina syndrome, but very few concerning unidirectional atraumatic needles. Holman and colleagues studied various injection rates through needles in a spinal cord model and recorded the distribution of hyperbaric dye using a digital video image technique.[17] He found that the injection rate had a significant effect on peak dye concentrations, and this could be modelled empirically by an inverse exponential formula. A slow injection directed caudally (2 and 4 ml min^{-1}) produced much higher concentrations of dye in the sacral distribution, whereas a fast injection produced lower concentrations of dye because of turbulence, resulting in more mixing and dilution. Interestingly, no further dilution occurred once a rate of 6 ml min^{-1} was exceeded, and this was similar whether the needle was a 24G Sprotte or a 27G Whitacre. Therefore, it is not surprising that Neigh and colleagues did not detect a difference in patients when he used a 22G Whitacre needle with the orifice pointing cephalad.[18] He injected hyperbaric tetracaine at 12 or 60 ml min^{-1}; both rates are in the turbulent range and therefore produce maximum mixing.[5 17]

Two other clinical studies looking at injection rates through Whitacre needles did show a difference in block characteristics between slow (1.2 ml min^{-1}) and fast rates (30 ml min^{-1}).[11 12] They both differed from our study because the patients were lying on their side and the needle orifice was pointing upwards, i.e. laterally to the spinal cord. Horlocker found that a slow injection of 0.3% bupivacaine (hypobaric) resulted in a peak sensory level that was four dermatomal segments lower.[11] Atchison and colleagues also found that a slow injection of hypobaric tetracaine produced a lower block level, which took longer to regress than the fast rate.[12] However, our *in vitro* observations support these findings, as with a slower injection there would be more flow in the direction of the orifice and consequently less lateral (cephalad and caudad) spread when the orifice is pointed perpendicular to the longitudinal axis of the spinal cord.[13]

Studies using hyperbaric solutions of local anaesthetic, even when using appropriately different injection rates, have not shown a difference in anaesthetic profile.[19 20] This is probably because the baricity of conventional 'hyperbaric' solutions is so excessive that gravity effects override all other effects.[21]

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LABORATORY INVESTIGATION

Comparison of relaxant effects of propofol on methacholine-induced bronchoconstriction in dogs with and without vagotomy

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Propofol has been suggested to have *in vivo* airway relaxant effects, although the mechanism is still unclear. In this study, we determined whether propofol could antagonize methacholine-induced bronchoconstriction and determined whether vagotomy modifies this relaxant effect. Fourteen mongrel dogs anaesthetized with pentobarbital and pancuronium were assigned to a control group (*n*=7) and a vagotomy group (*n*=7). The trachea was intubated with a special endotracheal tube that had a second lumen for insertion of the bronchoscope. Bronchial cross-sectional area, which was monitored continuously through the bronchoscope, was measured with image analysis software. Bronchoconstriction was elicited with methacholine (0.5 μg kg^{-1} + 5.0 μg kg^{-1} min^{-1}) until the end of the experiment. Thirty minutes after the start of methacholine infusion, propofol 0, 0.2, 2.0 and 20 mg kg^{-1} was administered. Changes in bronchial cross-sectional area were expressed as percentages of the basal area. Plasma concentrations of propofol and catecholamine were measured by high-performance liquid chromatography. Maximal inhibition (bronchoconstriction = 0%, baseline = 100%) and IC_{50} (concentration producing 50% inhibition of maximal effect) produced by propofol was obtained from each concentration–response curve using a curve-fitting program. Methacholine decreased bronchial cross-sectional area to 49.3% (95% confidence interval 38.5–60.1%) and 45.3% (34.8–55.7%) of the baseline value. Propofol 20 mg kg^{-1} significantly reversed this effect: bronchial cross-sectional area was reduced to 77.8% (66.2–89.6%) and 75.9% (64.0–87.9) in the control and vagotomy groups respectively. The two groups did not differ significantly in the maximal inhibitory effect of propofol [control group, 61.1% (46.3–75.9%), vagotomy group, 64.2% (40.1–88.3%)] or pIC_{50} [control group 5.03 (4.55–5.51), vagotomy group 4.86 (4.49–5.24)]. Therefore, the relaxant effects of propofol on methacholine-induced bronchoconstriction may not be mediated centrally. Propofol may relax airway smooth muscles directly or through the peripheral vagal pathway.

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Keywords: anaesthetics i.v., propofol; receptors, muscarinic; surgery, vagotomy; airway, muscles; equipment, bronchoscopes

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Propofol may produce anticholinergic effects on the airway as clinically it has been reported to prevent bronchospasm produced by tracheal intubation or fentanyl administration compared with thiopental in patients either with or without asthma[1–3] and produce bronchodilation in chronic obstructive pulmonary disease patients under mechanical ventilation.[4] In addition, using mongrel dogs, we previously reported that propofol decreased basal airway tone similarly to atropine and attenuated histamine-induced bronchoconstriction, and that this relaxant effect may be due to a reduction in vagal tone.[5]

On the other hand, *in vitro* studies suggest direct relaxant effects of propofol on airway smooth muscles. The mechanism has been suggested to be through reduction in intracellular Ca^{2+} concentration by block of L-type voltage-sensitive Ca^{2+} channels[6] and inhibition of Ca^{2+} release from intracellular stores,[7] but not by decreased Ca^{2+} sensitivity.[8]

Similarly, volatile anaesthetic agents have also been reported to produce airway relaxation by vagolysis and more direct actions.[9 10] Regarding the neural mechanism, several reports[9 10] suggest that inhibition of the peripheral vagal motor pathway may be involved.

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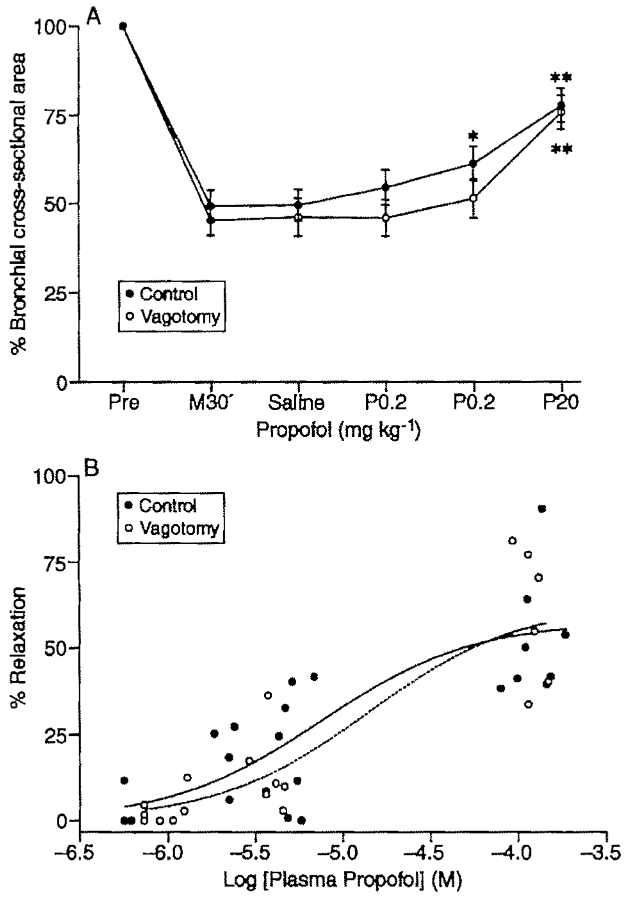

Fig 1 (A) Effect of propofol on methacholine-induced bronchoconstriction. Data are mean and SEM. M30′=30 min after start of methacholine infusion; 0=saline i.v. $*P<0.05$, $**P<0.01$ *vs* M30′. (B) Dose–response curve for relaxant effect of propofol. Relaxation is expressed as a percentage [peak constriction by methacholine=0%, full relaxation (baseline)=100%]. Solid circles, solid line=control group; open circles, broken line=vagotomy group.

Muscarinic receptors play an important role in cholinergic effects on the airway,[11] and previous reports suggest that muscarinic receptor subtypes m1, m2 and m3 exist in the human airway.[12] The m1 receptors facilitate neurotransmission through parasympathetic ganglia and enhance cholinergic reflexes. Activation of m3 receptors produces contraction of airway smooth muscles. Activation of m2 receptors inhibits the release of acetylcholine and may also counteract the bronchodilation produced by β-agonists.[12] Methacholine is a non-selective muscarinic receptor agonist,[13] and has been used clinically to quantitate airway responsiveness in asthmatic patients.[14]

In this study, we determined whether propofol could antagonize the muscarinic receptor-activated bronchoconstriction induced by methacholine. In addition, we compared the relaxant effects in normal dogs with those in vagotomized dogs to determine whether the relaxant effects are centrally mediated.

Methods

Our study protocol was approved by the Animal Care and Use Committee of the University of Hirosaki School of Medicine. Fourteen mongrel dogs (8–12 kg) were anaesthetized with i.v. pentobarbital (30 mg kg^{-1} + 2.0 mg kg^{-1} h^{-1}) and assigned to a control group (n=7) or a vagotomy group (n=7). The tracheas were intubated with endotracheal tubes (internal diameter 7.0 mm; Univent Tube, Fuji System, Tokyo, Japan) that had a second lumen for the insertion of a superfine fibre-optic bronchoscope. Neuromuscular block was obtained with pancuronium 0.2 mg kg^{-1} h^{-1} for mechanical ventilation with oxygen using a volume-controlled respirator (Servo 900C), and end-tidal carbon dioxidewas maintained at 4.0–4.5%. The femoral artery was cannulated to monitor arterial blood pressure and for blood sampling. The femoral vein was also cannulated for the insertion of a double lumen catheter, through which fluid and drugs were administered. In the vagotomy group, the vagus nerves were isolated and then cut bilaterally.

The cross-sectional area of third bronchial bifurcation in the right lung was monitored via a superfine fibre-optic bronchoscope (outside diameter 2.2 mm, AF type 22A; Olympus, Tokyo, Japan) to assess bronchial tone, as reported previously.[5] [15–18] Briefly, the image of the third bifurcation was printed with a video printer (VY-170; Hitachi, Tokyo, Japan) during the end-expiratory pause, and was then loaded into a Macintosh computer (Power Macintosh 7100/80 AV, Apple Computer, CA, USA) via a scanner (Scan-Jet 4c; Hewlett Packard, CO, USA) to measure bronchial cross-sectional area with image analysis software (MacScope 2.56; Mitani, Fukui, Japan). Image processing was performed by an investigator who was blinded to the study protocol.

Bronchoconstriction was elicited by i.v. infusion of methacholine (0.5 μg kg^{-1} + 5 μg kg^{-1} min^{-1}) until the end of the experiment. Initially we confirmed that this bronchoconstriction could be fully reversed by atropine. Thirty minutes after the start of methacholine infusion, the following doses of propofol were given at 10 min intervals in the order indicated: 0 (saline), 0.2, 2.0, 20 mg kg^{-1}. Bronchial cross-sectional area was measured before and 30 min after methacholine infusion started and 5 min after each propofol dose. Bronchial cross-sectional areas are presented as percentages of basal.

Arterial blood samples (6 ml) were centrifuged immediately at 3000 r.p.m. for 10 min at −10°C to separate plasma, which was then frozen at −70°C until measurement of catecholamines and propofol concentrations by high-performance liquid chromatography.[19] [20] The lower detection limits were 15 pg ml^{-1} for norepinephrine, 20 pg ml^{-1} for epinephrine and 100 ng ml^{-1} for propofol. The intra-assay coefficient of variation was 3.3% for norepinephrine, 6.0% for epinephrine and 2.9% for propofol.

Table 1 Changes in plasma catecholamine concentrations. Mean (95% confidence interval). M30 = 30 min after start of methacholine infusion, *P<0.01 *vs* M30

	Group	**M30**	**Propofol (mg kg^{-1})**			
			0	**0.2**	**2.0**	**20**
Norepinephrine (pg ml^{-1})	Control	295 (177–412)	324 (195–453)	322 (198–446)	276 (154–397)	107 (56–157)*
	Vagotomy	315 (200–429)	326 (196–455)	300 (195–405)	265 (157–372)	115 (88–142)*
Epinephrine (pg ml^{-1})	Control	182 (70–293)	214 (82–346)	210 (65–355)	131 (31–300)	54 (13–94)*
	Vagotomy	212 (53–371)	230 (42–417)	200 (47–353)	165 (31–300)	47 (10–84)*

Statistical analysis

All data are expressed as mean (95% confidence interval). Data were analysed by repeated measures analysis of variance followed by Fisher's protected least significant difference test using StatView II on a Macintosh computer. P<0.05 was considered significant. To obtain a concentration–response curve for propofol-induced relaxation, relaxation was expressed as a percentage: peak constriction by methacholine=0% and full relaxation (baseline)=100%. The sigmoid concentration–response curve was fitted using GraphPad Prism 1.03, and the maximal inhibition and –log of the concentration (μM) producing 50% inhibition of maximal effect (pIC_{50}) of propofol were obtained from each concentration–response curve.

Results

Plasma propofol concentration 5 min after 0.2, 2.0 and 20 mg kg^{-1} of propofol i.v. was 1.50 (0.69–2.30), 5.31 (4.52–6.10) and 126.0 (92.6–159.3) μM respectively in the control group and 0.95 (0.73–1.18) and 3.90 (3.35–4.46) and 125.2 (107.3–143.1) μM in the vagotomy group. Plasma concentration after propofol 2.0 mg kg^{-1} i.v. was significantly different between groups (P<0.01).

Methacholine decreased the bronchial cross-sectional area to 49.3 (38.5–60.1) and 45.3 (34.8–55.7)% of the basal bronchial cross-sectional area in the control and vagotomy groups respectively. In the control group, propofol 2.0 and 20 mg kg^{-1} significantly increased bronchial cross-sectional area, to 61.2 (49.4–73.1) and 77.8 (66.2–89.6)% of basal respectively (Fig. 1A). Similarly, in the vagotomy group the bronchial cross-sectional area was significantly increased to 75.9 (64.0–87.9)% of basal after propofol 20 mg kg^{-1} but not significantly after 2.0 mg kg^{-1} (Fig. 1A).

Maximal inhibition of methacholine-induced bronchoconstriction by propofol in the control and vagotomy groups, from the sigmoid concentration–response curve of propofol-induced relaxation, was 61.1 (46.3–76.9) and 64.2 (40.1–88.3)% respectively. The pIC_{50} of propofol in the control and vagotomy groups was 5.03 (4.55–5.51) (mean 9.3 μM) and 4.86 (4.49–5.24) (13.8 μM) respectively. There were no significant differences in maximal inhibition and IC_{50} between groups (Fig. 1B).

Plasma catecholamine concentration was significantly reduced after propofol 20 mg kg^{-1} i.v. in both groups, and the reduction in plasma catecholamines did not differ between groups (Table 1).

Discussion

We have reported previously that the relaxant effect of propofol may be due to vagolysis.[5] In the present study, as the spasmolytic effects of propofol did not differ between vagotomized and intact dogs, the spasmolytic effects of propofol on methacholine-induced bronchoconstriction may not be mediated centrally. Therefore, the relaxation could be due to inhibition of the peripheral vagal motor pathway or to direct inhibition. In addition, Brown and Wagner[21] reported that bronchoprotective effects of propofol *in vivo* as a local infusion via the bronchial artery attenuated vagal nerve stimulation-induced bronchoconstriction.

Figure 1B shows that the *in vivo* relaxant effect of propofol is concentration-dependent, and the clinical concentration (about 30 μM)[22] may reverse methacholine-induced bronchoconstriction by 45%. Azizkhan and colleagues[23] reported that tracheal cross-sectional area in respiratory symptomatic paediatric patients with a mediastinal mass was decreased by 35–93% of the normal tracheal dimensions. Huysmans and colleagues[24] studied the effectiveness of radioiodine therapy in patients with a large goitre compressing the trachea. They found that the tracheal cross-sectional area of the smallest lumen increased by 36% after therapy, and clinical symptoms such as dyspnoea and inspiratory stridor improved in eight of 12 patients. Therefore, 45% relaxation by clinical concentrations of propofol in the present study may be clinically significant.

In this study, propofol 2 mg kg^{-1} significantly reversed bronchoconstriction in the control group, but the reversal effect was not significant in the vagotomy group. However, plasma propofol concentration after 2 mg kg^{-1} i.v. was significantly higher in the control group than in the vagotomy group. In addition, as described above, there were no significant differences between the groups in maximal inhibition and IC_{50}. Therefore, vagotomy may not alter the relaxant effects of propofol, although we cannot explain the difference in plasma propofol concentration.

Direct relaxant effects of propofol should also be considered. As methacholine predominantly activates muscarinic receptors rather than nicotinic receptors, it is possible that propofol inhibits muscarinic receptor responses directly. Similarly, we reported previously that propofol concentration-dependently shifts the concentration–response curve of carbachol-induced contraction of guinea-pig tracheal smooth muscle.[25] However, using a radioligand binding assay, Lin and colleagues[7] reported that propofol (<100 μM) may not interact with muscarinic receptors in airway smooth muscles, although propofol 300 μM significantly decreased the binding affinity of $[^3H]$*N*-methyl-scopolamine to muscarinic receptors. It was also reported that propofol reduced the intracellular Ca^{2+} concentration in airway smooth muscle cells by inhibition of Ca^{2+} influx and of Ca^{2+} release from internal stores. Similarly, Yamakage and colleagues[6] showed that more than 10 μM of propofol significantly reduced Ca^{2+} current through voltage-sensitive Ca^{2+} channels in the airway smooth muscle cells. These data suggest that inhibition of Ca^{2+} mobilization by propofol may be involved in the direct relaxant effects.

Pancuronium was infused to prevent spontaneous respiration and bucking in the present study. As pancuronium has been reported to inhibit m2 rather than m1 or m3 receptors,[26] pancuronium may antagonize activation of m2 receptors by methacholine. Although m2 activation causes a reduction in acetylcholine release, the main mechanism of methacholine-induced bronchoconstriction is via m3 activation. In addition, although m2 receptors also counteract β-agonist-induced relaxation, propofol reduced plasma epinephrine concentrations in the present study. Therefore, pancuronium infusion may not attenuate methacholine-induced bronchoconstriction.

In the present study, plasma catecholamines were significantly reduced by propofol. This is consistent with a previous paper which showed that propofol produces sympatholysis more potently than vagolysis.[27] As the direct neural supply of the sympathetic system is limited in the lung, sympathetic influence on the airway tone is dependent on the plasma concentration of catecholamines.[28] Therefore, plasma catecholamines, especially epinephrine, may modulate airway smooth muscle tone. Indeed, we observed previously that histamine-induced bronchoconstriction was worsened by phenylephrine[16] and lidocaine,[17] with a reduction in plasma catecholamines, and reversed by droperidol[15] and divalent cations (Mg^{2+} and Zn^{2+})[18] with an increase in plasma catecholamines. Therefore, the decrease in plasma catecholamines may partially antagonize the relaxant effects of propofol.

In conclusion, the present data suggest that propofol inhibits methacholine-induced bronchoconstriction, but relaxation is not mediated via a central vagal pathway. This result is consistent with clinical reports suggesting potential bronchoprotective effects of propofol. However, it remains to be determined whether the relaxant effects are mediated through the peripheral vagal motor pathway or via direct actions.

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BJA

REVIEW ARTICLE

Anaesthesia and sleep apnoea

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> *Falstaff:*Now, Hal, what time of day is it, lad?
> *Prince Henry:*Thou art so fat-witted, with drinking of old sack, and unbuttoning thee after supper, and sleeping upon benches after noon . . .
> Act I, Scene II
> *Poins:*Falstaff!—fast asleep behind the arras, and snorting like a horse.
> *Prince Henry:*Hark, how hard he fetches breath . . .
> Act II, Scene IV
> *King Henry IV Part I*
> William Shakespeare

While the first detailed description of *obstructive sleep apnoea* (OSA) only appeared in 1966,[31] many had noted its characteristics prior to this. The best known of these descriptions is Dickens' portrayal of Joe the Fat Boy in *The Posthumous Papers of the Pickwick Club*, although it would seem that Shakespeare had observed the symptoms at least three centuries earlier. Considering Shakespeare's comic intent, it is clear that the audience would have been aware of them also. This suggests the problem to be a common one as several large studies now confirm.[11 120 139] These studies demonstrate that between 2 and 4% of middle aged adults have clinically significant sleep apnoea with a male:female ratio of 2:1.

Sleep apnoea is of particular concern to anaesthetists. The patient with disordered breathing during sleep is likely to also have disturbed breathing when sedated. This effect is compounded by sedation-related compromise of arousal, the mechanism that protects the sleeping patient from life threatening consequences of a breathing disturbance. Furthermore, the upper airway abnormalities that predispose to breathing obstruction during sleep may also make tracheal intubation difficult.

This review is presented in three sections. In the first, sleep-related breathing disorders are defined and the pathophysiology, clinical features, and management discussed. In the second, the nature of sleep and anaesthesia and their effects on ventilation are considered and in the third, the anaesthetic management of patients with sleep apnoea examined.

Sleep-related breathing disorders

Definitions

Disappointingly, there is as yet no broad consensus regarding standard definitions, including thresholds of significance, for many of the terms used to describe sleep-related breathing disturbances, although a recent report has addressed these issues.[4] It is generally agreed that an *apnoea,* defined as a cessation of airflow, has to exceed 10 s duration to be considered significant. No standard definition of an *hypopnoea* exists. It is usually defined as a reduction in airflow or respiratory effort for more than 10 s accompanied by a desaturation of 3% or more and/or electroencephalographic evidence of arousal.[4 126] The *apnoea hypopnoea index* (AHI) is the number of apnoeas and hypopnoeas per hour of sleep and is used more or less interchangeably with the term *respiratory disturbance index.*

The apnoeas may be obstructive, central or mixed. Obstructive apnoeas are characterized by persistent effort without airflow, while with central apnoea, effort is absent. OSA, where the apnoeas are predominantly obstructive or mixed, is much more common than *central sleep apnoea. Sleep disordered breathing* is a term commonly used to encompass both these and other related conditions, some of which are mentioned below. The term *obstructive sleep*

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apnoea syndrome is applied when OSA is accompanied by daytime sequelae such as excessive daytime sleepiness.

As there is a continuum of possible AHIs from trivial to severe, defining the presence of clinically significant sleep apnoea is somewhat arbitrary. It is generally agreed that the AHI should exceed five to be considered significant, with some advocating an AHI of 10 or more. It has been suggested that an AHI of five to 15 represents mild sleep apnoea, 15–30 moderate and greater than 30, severe.[4] However, the magnitude of associated symptoms and hypoxaemia also need to be considered when severity is determined.[77]

Hoffstein and Szalai[51] found that even with the inclusion of a 'clinical impression' by the examining sleep physician, clinical features could not reliably predict the presence or otherwise of OSA. Many patients, brought along to clinics by concerned bed partners who have witnessed apnoeas, deny symptoms. Conversely, some patients exhibiting all the daytime features of OSA have few apnoeas or hypopnoeas. Some of these habitual snorers have been found to have recurrent arousals from sleep resulting from increases in upper airway resistance not sufficient to cause apnoeas or hypopnoeas as usually defined, a condition now known as *upper airway resistance syndrome*.[45] Complicating matters still further is the variation in daytime sequelae, a few patients, and women in particular, presenting not with excessive daytime sleepiness but with other symptoms such as anxiety.[5] Nor do the above criteria always apply satisfactorily to children.[97]

Pathophysiology

OSA

A narrow, floppy upper airway provides the pathophysiological basis for OSA. This may have a congenital or acquired origin (Table 1). Usually such an airway does not cause problems during wakefulness. However, with sleep the associated loss of skeletal muscle tone makes the upper airway still narrower and floppier, particularly during rapid eye movement (REM) sleep when muscle relaxation is profound. This has two important consequences as gas is accelerated through it. First, the structures will tend to vibrate as turbulent flow patterns are produced, with snoring the result. Second, the pharynx will tend to collapse due to the Bernoulli effect, with resultant partial or complete obstruction. Obstruction will persist until sleep is interrupted and muscle tone is restored. Usually these interruptions are momentary arousals lasting less than 15 s and the sufferer is unaware of them. Occasionally, the obstructive event will result in an awakening, and the sufferer may complain of waking suddenly or with a snort or a snore. With arousal, breathing is restored and after a few breaths deeper sleep will resume with recurrence of the problem as the muscles again relax. In the more severe cases of OSA, this cycle of apnoeas and arousals may occur hundreds of times a night. In the more subtle cases, it may only occur in certain sleep stages (particularly REM sleep) and postures (particularly supine) or after alcohol consumption. The result of this constant sleep disruption is lethargy and somnolence during wakefulness.

Central sleep apnoea

Inadequate breathing during sleep due to diminished or absent respiratory effort (central sleep apnoea) may occur in association with disorders of ventilatory control or neuromuscular function or where the respiratory musculature is excessively loaded (Table 2). Patients with such conditions have diminished ventilatory capacity that may be sufficient for their needs during wakefulness but results in hypoventilation during sleep when the drive to ventilation is reduced and the compensatory mechanisms fail. Consequences

Table 1 Known and suspected predisposing conditions for obstructive sleep apnoea

Condition	Examples	Contribution
Obesity, body fat distribution[41 46]	Adult obesity, Prader-Willi syndrome	Complex and ill-defined
Race/genetics[6 92]		?Anatomical similarity
Age[13]		?Tissue laxity
Male gender[139]		Unclear
Alcohol,[123] sedatives, analgesics, anaesthetics		Muscle relaxation, depressed arousal
Smoking		?Chronic nasal congestion, pharyngeal oedema
Nasal obstruction[82]	Septal deviation, chronic nasal congestion	Increased pharyngeal negative pressure
Pharyngeal obstruction[47]	Tonsillar and adenoidal hypertrophy	Increased pharyngeal negative pressure
Cranio-facial abnormality[20 39 78 95 118 125]	Down's, Pierre-Robin, Treacher-Collins, Apert's, Crouzon's, Beckwith-Wiedemann, achondroplasia, acromegaly, fragile-X	Mid-face hypoplasia, macroglossia or micrognathia
Laryngeal obstruction	Laryngomalacia, tracheomalacia	Laryngeal collapse
Endocrine/Metabolic[40]	Hypothyroidism, androgen therapy, Cushing's	Upper airway infiltration or myopathy, obesity
Neuromuscular disorders[29 42 44 52 83]	Stroke, cerebral palsy, head injury, Shy-Drager, poliomyelitis, myotonic dystrophy, dysautonomia, tetraplegia	Disordered pharyngeal neuromuscular function
Connective tissue disorders[19]	Marfan's	Abnormal upper airway connective tissue
Storage diseases[109]	Mucopolysaccharidoses	Macroglossia
Chronic renal failure[63 73]		Unclear

Table 2 Known and suspected predisposing conditions for central sleep apnoea

Condition	Examples	Contribution
Neuromuscular disorders[32 52]	Poliomyelitis, amyotrophic lateral sclerosis, muscular dystrophy	Respiratory muscle weakness
Excessive respiratory load[41]	Obesity, airways disease, kyphoscoliosis	Excessive elastic, resistive or threshold loading of muscles
Disordered peripheral chemosensitivity[22 115]	Cardiac failure, bilateral carotid body excision	Delay or failure of ventilatory feedback from peripheral chemoreceptors
Disordered central ventilatory control	Stroke, head injury	Impaired ventilatory drive
Endocrine/metabolic[39]	Acromegaly	?Increased growth hormone and insulin like growth factor 1

Table 3 Symptoms associated with sleep apnoea

Adults	Children[47]
Heavy snoring	Snoring
Excessive daytime sleepiness	Restless sleeping
Witnessed apnoeas	Somnolence
Sudden awakenings with 'choking'	Aggression/behavioural problems
Accidents related to sleepiness	Hyperactivity
Poor memory/concentration	Odd sleeping postures
Delirium	Frequent coughs/colds
Gastro-oesophageal reflux	
Mood/personality changes	
Nocturnal sweating	
Restlessness during sleep	
Nocturia	
Enuresis (uncommon)	
Dry mouth on awakening	
Nocturnal or morning headache	
Impotence	
Nocturnal epilepsy	

Table 4 Signs associated with sleep apnoea

Oedematous soft palate or uvula
Long soft palate and uvula
Decreased oropharyngeal dimensions
Nasal obstruction
Maxillary hypoplasia
Retrognathia
Central adiposity/increased neck circumference
Hypertension and other cardiovascular consequences
Conditions/syndromes (listed in Tables 1 and 2) associated with sleep apnoea

include hypoxaemia, hypercarbia, sleep disruption and daytime somnolence. Unrecognized and untreated, polycythaemia and/or respiratory and right heart failure may supervene if sleep related hypoventilation is sufficiently severe. Similar consequences can accompany hypoventilation due to severe OSA.

Symptoms and signs

The key symptoms present in most cases of sleep apnoea are heavy snoring, occasional sudden awakenings that may be associated with momentary choking, apnoeas witnessed by a bed partner and excessive daytime sleepiness. Obtaining a history from the bed partner can be vital in eliciting several of these symptoms. Apart from these cardinal features, other recognized symptoms are listed in Table 3 and the signs in Table 4. While the symptoms lack specificity, in many cases a reasonably confident diagnosis may be made on history alone.

Investigation

The gold standard investigation for sleep apnoea is full overnight *polysomnography* (PSG) from which the type and severity of any apnoea may be determined. Electroencephalogram (EEG), electro-oculogram and submental electromyogram (EMG) are recorded for the purpose of staging sleep. Respiration is assessed by monitoring oronasal airflow (pressure transducer or thermistor), respiratory effort (inductance or impedance pneumography to monitor thoracoabdominal motion and/or diaphragmatic EMG) and pulse oximetry. Additionally, it is usual to monitor body position, sound and electrocardiogram. Videotape to record body movements and transcutaneous carbon dioxide are also used in selected cases. Subsets of these may be used for screening purposes, an example being the MESAM 4 system using oximetry, heart rate, snoring and position.[119]

Originally, the PSG data were printed out in real time using a polygraph. This method has now largely been replaced by digital storage techniques using a variety of commercially available software packages. Either way, the records are examined in 30 s 'epochs' and the sleep stage for each epoch is determined using the criteria of Rechtschaffen and Kales.[91] Respiratory events are scored using the definitions listed above and the total number of events, their duration and the degree of desaturation summarized for the whole night and for specific sleep stages.

Nasopharyngoscopy or upper airway imaging (lateral cephalometry or computed tomography) may be performed to guide treatment; for example, whether or not surgery will be of any benefit.

The results of these investigations are relevant for anaesthetists as they give some indication of the likelihood of difficulty with intubation or airway maintenance.

Sequelae

There are many sequelae of sleep apnoea which have limited relevance to anaesthesia. A variety of confounding

Table 5 Potential sequelae of sleep apnoea

Neuropsychological[58 59 71]	Sleepiness, impaired memory and cognition, decreased vigilance, increased accident risk, anxiety and depression, chronic headache, intracranial hypertension
Cardiovascular[17 53 56 68 74 135]	Hypertension, ischaemic heart disease, cerebrovascular disease, right heart failure
Pulmonary[72 106]	Hypoxaemia, hypercapnia, pulmonary hypertension
Endocrine[15 38]	Decreased growth hormone and testosterone levels, diabetic instability
GIT[62]	Gastro-oesophageal reflux

factors exists which make this issue a complex one.[69] The symptomatic accompaniments have already been listed (Table 3) and other sequelae are summarized in Table 5.

While yet unproven, several of the acute changes associated with apnoeic episodes have the potential to influence perioperative progress. Possible complications include arythmias, myocardial ischaemia, cerebrovascular insufficiency, intracranial hypertension, mental dysfunction and poor wound healing.[30 34 35 58 93 98 99 101]

Chronically, if the sleep apnoea is severe enough, respiratory and right heart failure may develop as the result of persistent, severe nocturnal hypoxaemia and hypercapnia, further increasing the risk of anaesthesia and surgery.

Treatment

OSA

In mild cases, conservative measures alone may lead to a satisfactory improvement. These measures include weight loss, reduction of alcohol or sedative consumption, sleeping laterally, and cessation of smoking. In most cases, however, these form an adjunct to more aggressive therapy, either because they are insufficient by themselves or because they prove difficult to achieve.[37] Trials of drugs that alter sleep architecture or upper airway muscle tone and electrical stimulation of the upper airway muscles during sleep have so far proved disappointing.

Introduced by Sullivan in 1981,[121] nasal continuous positive airway pressure (nCPAP) remains the treatment of choice for OSA of at least moderate severity.[36] This treatment is highly effective and prevents obstructive events by pneumatically splinting the upper airway.[90] Compliance, however, is variable and in milder forms of sleep apnoea, where daytime symptoms are mild, it is often not well accepted by patients, being moderately intrusive.[36]

In severe OSA, particularly when associated with morbid obesity or other coexisting disease such as chronic airflow limitation, the patient may present in respiratory and right heart failure. In addition to the obstructive apnoeas, central sleep hypoventilation can be present in such cases, particularly during REM sleep. If so, initial control is often best achieved with non-invasive bi-level ventilatory assistance. This involves the delivery of intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure via a nasal or face mask using BiPAP (*Bilevel positive airway pressure*) or similar device. Once control of sleep hypoventilation and respiratory failure have been achieved it is often possible to convert to CPAP, a cheaper therapy, if the predominant problem has been OSA.[89]

The use of oral appliances that reposition the mandible (forwards), increasing the pharyngeal dimensions, is becoming more common for the treatment of snoring and milder forms of OSA.[2 86] Potential complications of these devices such as temporomandibular joint dysfunction have not yet been widely investigated,[36] but there is now evidence that they are associated with dental side-effects which, while generally mild and temporary in nature, may necessitate treatment cessation in some individuals.[88]

Palatal surgery is a reasonable treatment alternative for habitual snoring but a less certain treatment for OSA.[1 3 37 110] Surgical correction of nasal obstruction is important but, of itself, does not usually result in resolution of sleep apnoea. Surgical removal of obstructing lesions in the pharynx can be definitive and tonsillectomy/adenoidectomy is a front-line treatment of obstructive sleep apnoea in childhood.[47] Maxillofacial surgery may be necessary where craniofacial abnormalities exist that are associated with OSA,[23] but its use is limited.[18] Tracheostomy, the main method of treating sleep apnoea prior to the development of CPAP, is now only indicated in life-threatening OSA when non-invasive forms of respiratory support are not tolerated.

Central sleep apnoea

Patients with sleep-related hypoventilation due to neuromuscular disease or one of the other causes listed in Table 2 may respond to treatment with CPAP or respiratory stimulants. More usually, if sufficiently severe, non-invasive ventilatory assistance is required and IPPV via nasal or face mask is the method of choice.[37] In those patients requiring IPPV for greater than 12 h a day and in patients with inadequate airway patency or protection, a tracheostomy may be necessary. External negative pressure ventilation, such as with a cuirass, may exacerbate or induce upper airway obstruction[49] and the cumbersome nature of this treatment has rendered it largely obsolete.

Sleep and anaesthesia–their nature and effects on ventilation

Sleep

Unlike anaesthesia, sleep is a state of *rousable* unconsciousness. While much is known about the electrochemical factors influencing sleep onset and the sleep–wakefulness cycle, the exact function of sleep remains unclear, apart from the fact that it is essential for wellbeing.

Electrophysiology of sleep

The EEG was first used to investigate and characterize sleep by Loomis and colleagues in the 1930s.[76] It was not until 20 yr later that Aserinsky and Kleitman recognized the association between eye movement and the phases of sleep[7] but this soon led to the definition of sleep stages based on EEG, eye movements and muscle tone, more or less as we now know them (non rapid eye movement (NREM) stages 1 through 4 and REM), by Dement and Kleitman in 1957.[24] Rechtschaffen and Kales subsequently refined these definitions into guidelines that remain the international standard after 30 yr of use.[91]

A single pair of EEG leads may be used to stage sleep. Typically, one electrode is placed adjacent to the vertex (C3 or C4) and another over the contralateral mastoid (A2 or A1). The differential input from these is referred to a third, often the other mastoid. An occipital electrode may also be used. For the eye movements, another pair of electrodes is used, one *above* the outer canthus of one eye, the other *below* the outer canthus of the other eye. Both are referred to one of the mastoids. This results in out-of-phase deflections for both horizontal and vertical eye movements, allowing differentiation from artefacts, which are usually in-phase. A third pair of electrodes is placed under the chin to monitor the EMG.

Relaxed wakefulness is characterized by sinusoidal alpha (8–12 Hz) and low voltage, mixed frequency activity on the EEG, accompanied by eye movements, blinking, and high submental EMG tone. With sleep onset (stage 1) there is muscle relaxation, slow horizontal rolling of the eyes and a marked reduction in the amount of alpha activity, leaving mainly the low voltage, mixed frequency component.

Stage 2 may be associated with a further reduction in the EMG, but it is particularly defined by the appearance, superimposed upon the stage one type EEG background, of sleep spindles (short bursts of 12–14 Hz activity similar to waking alpha) and K-complexes (a sharp negative wave immediately followed by a broader, high voltage positive component). K-complexes may be either spontaneous or a response to an external stimulus, and are frequently closely associated temporally with spindles.

Stages 3 and 4, together referred to as *slow wave sleep* (SWS), are characterized by high voltage delta (1–4 Hz) activity (hence its other less common name, *delta sleep*). If the epoch has between 20 and 50% of its record consisting of slow waves then it is scored as stage 3. Epochs containing more than 50% SWS are classified as stage 4.

Stage REM has an EEG pattern similar to stage 1. It is, however, clearly defined by the presence of episodic rapid eye movements, very low EMG amplitude and a variety of other physiological changes as described below.

The typical sleep pattern

Of the few previous depictions in the anaesthetic or surgical literature of the normal human sleep pattern,[61 103 104] at least one is somewhat inaccurate[104] and none mention the changes in this pattern with age. Knowledge of the typical pattern is necessary before assessment of perioperative changes can be made and as a number of assumptions and speculations have been drawn from relatively few observations of perioperative sleep this is all the more important.

In *young adults*[24 60 136] a brief initial period of stage 1 is usually followed by stages 2, 3 and 4 in that order. The SWS component normally predominates this first NREM period and after about 70 min of sleep the first REM stage occurs, preceded by a period of stage 2. This cycle is repeated, depending upon the total sleep time, up to six times but the later cycles usually lack stage 4. The REM periods tend to lengthen as sleep progresses while the cycle length, averaging 70–90 min, shortens as the NREM component decreases more than the increase in REM. Stage 2 is the predominant stage for the total period of sleep, usually making up about 50%. Stage 1 totals about 5%, SWS about 20% and REM about 25%. The graphical depiction of sleep in stages is known as the hypnogram and an example from a young adult male is shown in Fig. 1.

Influence of age

The changes in sleep pattern with age are profound[28] and have the potential to heavily influence interpretation of studies into perioperative sleep. Total sleep time shows a precipitous decline during adolescence from an average of 10 h day^{-1} or more at age 6 yr to about 7.5 h in early adulthood. There is then a plateau until old age when a further but less dramatic decline occurs. The proportion of time spent in bed but awake remains at a few per cent until mid-life whereafter it rapidly increases to about 20% or more in old age. The number of arousals per night increases more linearly. As a result of these changes ageing is associated with more frequent and prolonged interruptions to sleep.

REM sleep decreases from more than 50% of total sleep time in neonates[117] to about 30% in later childhood before a plateau of about 25% for most of adulthood and a further decline to about 20% late in life. Stage 4 sleep, on the other hand, displays no plateau, its total amount declining sharply during adolescence, then halving again between the ages of 20 and 60 yr. This decline in stage 4, about half of which normally occurs in the first sleep cycle on any given night, results in a shorter first cycle and hence a reduction in REM latency, the time to first REM onset. This first REM period also becomes longer in old age, leading to a more even distribution of REM throughout the sleep cycles, the number of which is about the only sleep variable to remain constant with age.

Other physiological variables in sleep

A complete account of the gamut of physiological changes during sleep is outside the scope of this work. Each stage of

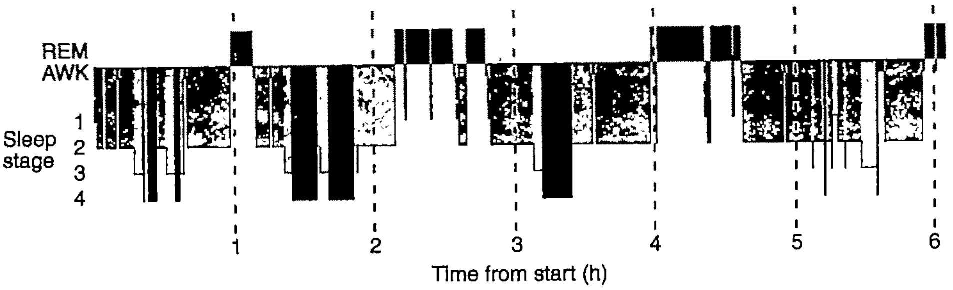

Fig 1 Actual hypnogram of a young adult male medical student—a graphical depiction of the sleep stages during one night's sleep (recorded and manually scored with a commercial sleep monitoring system; Compumedics, Melbourne, Australia). REM=rapid eye movement sleep; AWK=awake or movement time. The final REM period ended prematurely as a consequence of study termination.

sleep has a fairly distinct pattern of physiological phenomena[26 43] and the complexity is such that any attempt at classifying sleep stages according to some arbitrary measure of 'depth' amounts to gross oversimplification. Nevertheless, in order to examine the impact of sleep in the perioperative period knowledge of some of these changes is required.

Skeletal muscle function. All skeletal musculature, be it postural, chest or abdominal wall, diaphragm or upper airway, is subject to state-related activity changes. There are, however, marked differences between the groups. The tone of postural muscles, compared with wakefulness, is reduced somewhat in NREM and almost completely abolished in REM. This is a consequence of hyperpolarization of alpha motor neurones[108] which is most marked during the transition from NREM to REM sleep and during bursts of eye movement activity, commonly referred to as *phasic REM sleep.*[81] Despite this, phasic REM is characterized by rapid, random fluctuations in motor neurone membrane potential, hence varying levels of excitation and inhibition resulting in the eye movements and twitches of limbs and facial muscles. This occurs against the background active inhibition of *tonic REM sleep.* In contrast to non-respiratory muscles, the inspiratory activity of the chest wall, accessory and diaphragm muscles is preserved in NREM, as is the expiratory activity of the abdominal wall.[48 112 113 124] During REM, the tonic and phasic activity of all of these muscles except the diaphragm is greatly reduced. The diaphragm's phasic activity is preserved, albeit on a background of reduced tone.[128] This explains the profound hypoventilation seen when patients with diaphragmatic weakness enter REM sleep.[111] The upper airway musculature follows the same pattern as the postural muscles,[107] increasing the tendency to collapse,[55] especially during REM, but as some muscles are constrictors rather than dilators, and as the state-related changes differ from muscle to muscle and from individual to individual, this tendency may not be universal.

Ventilation-perfusion relationship. Functional residual capacity (FRC) is reduced during sleep, presumably as a consequence of sleep related changes in respiratory muscle tone together with gravitational effects of the supine position on the lung and abdominal contents.[54] This results in atelectasis in the dependent regions of the lung with shunt, particularly in the case of patients with obesity and chronic lung disease.[10]

Load compensation. The application of resistive or elastic respiratory loads during wakefulness leads to a rapid increase in the motor output to the respiratory musculature as well as an increase in the duration of inspiration.[57 134 137] In addition, increased negative pharyngeal pressure resulting, for example, from increased upper airway resistance leads to an increase in the neural output to upper airway dilator muscles.[79 132] Sleep not only imposes both resistive and elastic loads on the respiratory muscles, via upper airway narrowing and decreasing FRC, respectively, but it also compromises the compensatory mechanisms that cope with these changes. During NREM sleep, load compensation occurs but is slow and incomplete[7 134 137] with increased reliance on chemical drive which itself may be depressed (see below), the end result being a degree of hypoxaemia and carbon dioxide retention. The situation in REM is worse still, with a further increase in loading and a simultaneous failure of intercostal, accessory, upper airway dilator and expiratory muscles to assist in the necessary compensation. The coexistence of either neurological or mechanical respiratory disease, already challenging the compensatory mechanisms, further increases the tendency to hypoventilation.

Ventilatory control. Wakefulness has an important stimulatory effect on ventilation. While it appears that chemosensitivity is important for maintaining ventilation during sleep, as indicated by the increased sleep-related hypoventilation seen in patients with carotid body denervation,[22] the effects of sleep on chemoreception are far more complex and difficult to define. Standard tests of acute ventilatory responses have demonstrated varying degrees of inhibition, particularly of the response to combined hypoxia and hypercapnia, but these may overestimate the reduction in chemosensitivity as other factors such as increased upper airway resistance, impaired load compensation and changes in cerebral blood flow need to be considered.[26] On the other hand, sleep does unmask the 'apnoeic threshold', not normally seen in wakefulness.[25] Thus, in sleep, apnoeas or hypopnoeas can be produced by lowering the $P\text{CO}_2$, as may occur during hypoxic hyperventilation.[12] This reduction in ventilation may then result in an overshoot into hypoxic hypercapnia again, leading itself to hyperventilation and consequently a cycle of hypoxia-induced periodic breathing with large swings in oxygen saturation—a variant of *central sleep apnoea*. Ironically, sufficiently large increases in upper airway resistance may be one factor preventing periodic breathing in some subjects by limiting the hyperventilation.[26] Despite the lack of clarity with respect to sleep effects on chemosensation, it appears that there is a reduction in output from medullary respiratory neurones, particularly during NREM, whereas in REM the output from these neurones tends to be related to the variability in breathing pattern.[26] REM, however, is associated with a depression of the arousal responses to hypoxia and hypercapnia, leading to a tendency for apnoeas to be longer and desaturations more severe in that sleep stage.

Anaesthesia

In contrast to sleep, anaesthesia is a state of *unrousable* unconsciousness.

The electrophysiological nature of anaesthesia is an area of intense ongoing investigation, particularly now with devices allegedly able to monitor 'depth' of anaesthesia becoming available. It is, however, a very complex issue as different anaesthetic agents have different effects on the EEG[14] so that no unitary pattern indicating anaesthetic 'depth' exists. It is, therefore, very difficult to make any electrophysiologic comparisons between sleep and anaesthesia, although attempts are being made,[114] and such comparisons are probably irrelevant in any case, as the two states are quite distinct. With few exceptions, anaesthetic and sedative drugs produce a dose dependent depression not only of consciousness, but also of most other vital functions, including all those related to respiration. Apart from abolition of the stimulatory effects of wakefulness these include depression of hypoxic and hypercapnic responses,[116] load compensation reflexes[85]and the arousal responses that normally protect against asphyxia. As with sleep there is depression of skeletal muscle tone with reduction in FRC, predisposing to atelectasis, and upper airway muscle relaxation predisposing to obstruction. These effects are compounded by reduction in the phasic activity of intercostal and accessory respiratory muscles, increasing dependence on the diaphragm, and of the upper airway muscles during inspiration, further predisposing to obstruction as this activity acts to stiffen the airway as intraluminal pressure falls.[127]

The presence of a vigilant anaesthetist to monitor and maintain vital functions during anaesthesia protects the patient from these effects. However, drug induced sedation and post-anaesthesia drowsiness, where the borders between wakefulness, sleep and anaesthesia are less distinct and monitoring perhaps less rigorous, present great potential danger to the patient with a sleep-related breathing disorder because of the depression of these responses.

Sleep in the post–operative period

There has only been one study examining the effects of general anaesthesia alone (with isoflurane) on subsequent sleep and it would appear that this effect is negligible.[84] Other studies imply that the type of anaesthesia is also not important.[61 75] The addition of a surgical insult changes things considerably.[102] Sleep architecture is disrupted to a degree which is generally proportional to the 'magnitude' of the surgery as is the duration of the disruption, but it is important to note that there is considerable inter-individual variation and specific situations where the generalization may not hold. The disturbance takes the form of reduced total sleep time with a disproportionate reduction in REM and SWS.[8 61] At some point during the first postoperative week there is a rebound, firstly of total sleep time with mainly stage 2 usually, then a resurgence of REM ('REM rebound') and to a lesser extent SWS.[65 87]

The precise mechanism by which the surgical insult produces the sleep disruption is not completely clear but it is likely that pain plays a major role. Other factors, which may be independent of the surgery and thus account for some of the variability, are neuroendocrine, metabolic and psychological responses, opioid analgesia, and environmental factors such as noise, light and nursing activity.[75 102 105]

The extent to which these changes in sleep architecture after surgery influence morbidity and mortality is currently unknown but there has been considerable speculation based on indirect evidence.[102 104] Patients with REM predominant apnoea, for example, might be expected to have an increase in the number and degree of desaturations over a night where REM rebound is occurring[103] but this possibility has been inadequately investigated. Similarly, the occurrence of REM rebound has led to the suggestion that an associated late postoperative increase in nocturnal hypoxaemia could be contributing to mental confusion, wound breakdown, myocardial ischaemia and infarction, stroke and death.[34 35 93 98–101] While some relevant associations have been demonstrated direct evidence of causation is lacking.

While anaesthesia, of itself, may not effect subsequent sleep once the anaesthetic agents are eliminated, a considerable amount of research over the last 20 yr has considered the effects of subanaesthetic concentrations on sleep and ventilatory control. Commencing with the work of Knill's group in the 1970s,[64] conflicting results have emerged regarding the effects on ventilatory responses to hypoxia and hypercapnia of subanaesthetic concentrations of potent inhalational agents, such as might be present in the minutes to hours after emergence,[33] as well as some other drugs commonly used perioperatively. One reason for these conflicts appears to be the effect of sleep as van den Elsen, Dahan and colleagues have shown that subjects stimulated and kept awake exhibited more or less normal ventilatory responses despite the presence of the potent inhalational agent whereas those allowed to sleep exhibited ventilatory depression.[130 131] The mechanism by which sleep might contribute to the depression of ventilatory responses by sedative agents has not yet been investigated.

Anaesthesia and sleep disordered breathing

Perioperative risks for sleep apnoea

Notwithstanding the relative paucity of specific information, knowledge of their physiological effects strongly suggests that anaesthetic, sedative and analgesic agents will aggravate or precipitate OSA by decreasing pharyngeal tone, depressing ventilatory responses to hypoxia and hypercapnia and inhibiting arousal responses to obstruction, hypoxia and hypercapnia. These latter effects frequently result in varying degrees of central respiratory depression.

A variety of surgical factors are also contributory. Surgery of the thorax and upper abdomen compromises ventilatory function,[27 66] potentially compounding the effects of any OSA or centrally mediated hypoventilation that might occur postoperatively. Surgery involving the upper airway carries the risk of postoperative swelling that can worsen or precipitate obstruction.[16 70 80 18] The same applies to situations where the nose is packed or a nasogastric tube is required, as the reduced lumen calibre will necessitate the generation of more negative pharyngeal pressures during inspiration thus promoting collapse.[122] They may also compromise therapy by making nasal CPAP difficult or unusable, and a full-face mask may be required in such circumstances. Patients are frequently nursed supine, sometimes for good reason, and as OSA is often position-dependent this, too, may contribute to increased risk of upper airway obstruction.

To whom might these risks be important?

OSA is common and anaesthetists will often deal with sufferers. There are those who present having already been diagnosed with the disorder. The majority of this group will be on some sort of treatment, usually CPAP, but with a variable degree of compliance.[36] Some will bring their CPAP machines with them to hospital while others will arrive without their equipment, seemingly quite prepared to forego treatment for the duration of their hospital stay. It can reasonably be assumed that many in this latter group are poorly compliant at home. Another group will have been diagnosed with sleep apnoea but either declined treatment from the start or failed a trial of therapy.

There are still a large number of people who present for surgery with features suggestive of sleep apnoea but who have either never even heard of the condition and/or have not sought diagnosis or treatment. There is also a final group of patients who have apnoea but either lack the overt features or have features that are missed perioperatively. Given the high prevalence of OSA in the community, there appears to be little doubt that the number of patients in these last two groups far outweighs the number having already been diagnosed.

Suspected or undiagnosed apnoea

Enquiry about snoring and sleep should be a routine component of the preoperative visit. Patients should be asked about common symptoms: heavy snoring with, perhaps, sudden awakenings associated with a choking sensation or similar; witnessed apnoea by a bed partner; waking unrefreshed in the morning perhaps even with a headache; excessive daytime sleepiness. These symptoms should particularly be sought in obese patients, middle aged and older patients and in patients with conditions leading to narrowing of the upper airway such as nasal obstruction, tonsillar hypertrophy, or retrognathia. Where difficult intubation is anticipated the possibility of sleep apnoea should also be entertained.[50] The presence of otherwise unexplained respiratory or right heart failure or polycythaemia might also point to undiagnosed (and severe) sleep apnoea.

In cases of suspected sleep apnoea, especially if thought to be severe, deferral of the surgery should be considered to enable investigation and, where indicated, institution of treatment preoperatively. In many instances, the delay this entails would be inconvenient or, in the case of emergency surgery, impossible. Where available and practicable, preoperative consultation with a sleep physician may allow a sleep study to be performed and the problem defined and treated at short notice. If not, perioperative management should be planned on the basis that the patient has the condition, according to the principles outlined in the following section with an intention to refer the patient for definitive investigation at the earliest opportunity.

Anaesthetists are in an excellent position to screen patients for sleep apnoea and as it can be associated with substantial morbidity it is a responsibility they should not ignore. A clinical suspicion of sleep apnoea may first develop at the preoperative consultation, intraoperatively (if the patient proves difficult to intubate or it is difficult to maintain the airway[50]) or postoperatively with snoring and obstruction observed in the recovery room and/or beyond. These considerations are as important to children as they are to adults, with growth and development potentially compromised by untreated sleep apnoea.[96]

Diagnosed apnoea

The preoperative assessment of patients where the diagnosis of sleep apnoea has been made should be used to establish the severity of the sleep apnoea, mode of treatment, compliance with and complications of treatment, complications of the apnoea itself and conditions the patient might have which are the cause of or otherwise associated with the apnoea.

OSA is, by definition, an airway problem and its presence may indicate a predisposition to difficulty with intubation or airway maintenance under anaesthesia. Severity of sleep apnoea may be an important predictor of these difficulties. While there are good theoretical grounds on which to suspect these associations, it is important to note that, at the current state of knowledge, they remain speculative. Prudent anaesthetic management is guided by awareness of these possibilities.

The anaesthetic management plan is determined by the severity of sleep apnoea, how it has been managed prior to anaesthesia, the planned surgical procedure and the likely postoperative analgesic requirements. In the case of mild OSA, managed conservatively (without CPAP) presenting for a simple procedure with little anticipated postoperative discomfort, an anaesthetic technique which either avoids unconsciousness or ensures its early recovery together with close observation and nursing in the lateral posture during the early recovery process may be the only specific measures necessary. In contrast, the patient with severe OSA who has substantial analgesic requirements will need close supervision in a high dependency area postoperatively and use of nasal CPAP whenever sedated or otherwise asleep. Such patients particularly may benefit from regional anaesthetic and analgesic techniques, the potential benefit increasing with OSA severity, although complications of such techniques have occurred in this setting.[67]

Provision for 'the worst case scenario' of persistent upper airway obstruction should be made even with patients with mild OSA and a breathing circuit capable of delivering CPAP should always be available when the presence of OSA is known or suspected.

Preoperative preparation. Patients with diagnosed apnoea who are being treated with CPAP should take their equipment to the operating theatre with them for use postoperatively. These arrangements should be discussed with the patient. There are psychological as well as physiological aspects to consider. While less compliant patients may care little, there are many that are very concerned at the idea that they may stop breathing. The knowledge that their CPAP machine is available is likely to be important to them.

Attending staff must understand the use of the CPAP machine so that they are able to apply it to the patient while he/she is unable to apply it him/herself. While this knowledge may be commonplace amongst the nursing staff of some hospitals it should not be assumed. Staff should be instructed in its use prior to surgery, the patient demonstrating its function if necessary. Hospitals with their own sleep units will have nurses and/or technologists who are familiar with CPAP therapy and able to render assistance where required. This should be established beforehand and the hospital's sleep unit may have CPAP machines available to loan where needed.

It has been argued that sedative premedicants should be avoided in OSA patients.[21 133] Certainly it is sensible to exercise some care with premedication but in those patients on CPAP there is no real contraindication to even quite heavy premedication as their CPAP may be applied if they get sleepy and oxygen can be added if necessary.[94] It is appropriate to monitor oxygen saturation and for the patient to be observed. An unsupervised holding area is inappropriate for a premedicated sleep apnoea patient. If more than light premedication is prescribed then an i.v. cannula should be placed in case antagonists are required urgently. Appropriate antagonists should be immediately available. Some authors have suggested aspiration prophylaxis[21] and the possibility of airway difficulty may justify the use of antisialogogues in these patients.[133]

Intraoperative care. Choice of anaesthetic technique is important. The problems of airway maintenance intra- and postoperatively and suppression of arousal responses can be circumvented by use of regional techniques. If the surgical procedure lends itself to them and the patient is otherwise suitable they should be considered, bearing in mind the necessity for airway management should the regional technique result in unconsciousness or respiratory paralysis. If general anaesthesia is necessary then the following considerations apply.

Preparation for a possible difficult intubation should be made along with strategies to manage what may be a difficult airway intraoperatively if the patient is not to be intubated. The choice of induction and maintenance agents is probably not important although it would seem sensible to avoid large doses of longer acting drugs, especially neuromuscular blocking agents. Opioids should be used judiciously although the availability of CPAP will obviate potential difficulty postoperatively, particularly if the patient is already familiar with it. The issue of familiarity is important, as the early postoperative period is not the ideal environment for introduction of CPAP therapy, particularly if the patient is restless, in pain or hypoxaemic.

Postoperative care. In the recovery room and the postoperative ward the patient should be nursed in the lateral posture because of the particular tendency to upper airway obstruction when supine. A nasopharyngeal airway can be a useful aid during emergence.[138] Nasal CPAP should be applied where obstruction persists despite these simple measures.

Oxygen therapy alone is not an adequate treatment of OSA as the issues of recurrent arousals and of carbon dioxide retention remain. The absence of recurrent desaturation may also act to mask the presence of obstructive episodes, particularly in the presence of an inexperienced observer. Oxygen can be added to CPAP treatment. The most economical place to add it is via a side port on the CPAP mask where relatively low flows (2–4 litre min^{-1}) can produce a high $F\text{I}_{\text{O}_2}$. This addition does not change the CPAP pressure supplied by most modern machines.

The potential problems associated with the use of postoperative sedatives may be circumvented by the use of regional analgesia and/or non-steroidal analgesics or, if opiates are needed, effective use of CPAP.

It is important that the patient with OSA is nursed in the appropriate postoperative environment. This issue is closely related to the patient's analgesic requirements. For the patient who requires CPAP therapy direct supervision is needed while sedated or otherwise asleep until they are capable, unaided, of applying their therapy correctly. This may require admission to a high dependency unit for one or more days postoperatively, particularly for those patients not already familiar with CPAP therapy. On the other hand, patients who recover quickly from general anaesthesia and have little narcotic or sedative requirement, or who have good regional analgesia, may be in a position to manage their own CPAP therapy immediately following discharge from the recovery room with no need for special nursing. Where upper airway surgery has been performed, especially in the case of children, high dependency care is warranted. Postoperative swelling has been known to exacerbate apnoea after adenotonsillectomy or uvulopalatopharyngoplasty[16 80] and death due to obstruction has occurred after velopharyngeal repair of cleft palate.[70 129] If serious compromise of upper airway patency is anticipated after upper airway surgery then undue reliance on CPAP is inappropriate. The patient may require prolonged tracheal intubation or, where several days or more of airway compromise is anticipated, tracheotomy.

Patients with nasogastric tubes and those having nasal surgery present a special difficulty. The presence of a nasogastric tube does not preclude the application of CPAP as the nasal mask can be applied over the tube, which runs under the mask cushion, but leakage and comfort may be a problem. Patients who have had nasal surgery performed are problematic, particularly if their noses have been packed. A nasopharyngeal airway may be tolerated and it may also be possible to have the surgeon pack the nose around it, although it may have limited calibre. CPAP may need to be applied via a full face rather than nasal mask in such cases.

Summary

Sleep disordered breathing is a common problem affecting all age groups, particularly in association with certain other medical conditions and syndromes. The pathological consequences of the disorder may be severe, with significant implications for the perioperative management of sufferers.

Research into the effects of surgery and anaesthesia on sleep is very much in its infancy. Understanding of the implications of sleep disturbance and sleep disordered breathing for perioperative morbidity and mortality is limited. While several observations have led to considerable speculation in the literature, evidence of a causal relationship is still largely lacking.

Anaesthetists are ideally placed to screen large numbers of people for sleep disordered breathing, a source of considerable community morbidity. Recognizing the symptoms, signs and associations of the condition during the preoperative visit is important in planning management, as is recognition of the likelihood of OSA in patients who present difficulty with tracheal intubation or airway maintenance. Particular care is required in the perioperative management of patients with diagnosed or suspected sleep apnoea.

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SHORT COMMUNICATIONS

Renal effects of inhaled nitric oxide in humans

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We measured renal sodium and water excretion in five healthy male volunteers who inhaled nitric oxide. Urine volumes, urinary sodium and creatinine, and plasma sodium and creatinine were measured before, during and after a 2-h period inhaling nitric oxide (40 vpm in air). A control experiment, excluding the nitric oxide, was done on a separate day. Nitric oxide increased urinary volume (mean increase 85%, SEM 22%) and prevented a decrease in fractional excretion of sodium (32% SEM 8%) seen in the control experiments, without a detectable change in creatinine clearance. The results suggest the inhaled nitric oxide may alter tubular salt and water resorbtion in humans. The mechanism for this remains unclear.

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Inhaled nitric oxide (iNO) is used to treat acute pulmonary hypertension and to improve pulmonary ventilation/perfusion relationships in critically ill adults and children. The effects of iNO have always been considered to be restricted to the lungs as it is metabolized before it leaves the pulmonary circulation.[1] In volunteer studies no effects are seen in systemic haemodynamics.[2] However, a recent study of the effects of iNO on phenylephrine-induced pulmonary hypertension in anaesthetized pigs[3] found that iNO might have renal effects. In the control animals, where iNO was given to anaesthetised normal pigs, a marked diuresis was found and could not be accounted for by any changes in global haemodynamics.

We studied the renal effects of iNO in humans to determine if a similar effect occurred.

Methods and Results

Five healthy non-smoking male volunteers aged 18–41 yr and weighing 75–90 kg were studied. Approval was obtained from Central Oxford Research Ethics Committee and the subjects gave written consent.

The experiment consisted of three 2-h phases: a control phase with subjects breathing room air normally, a middle phase breathing an NO/air mixture through a mask, and a second control phase breathing air normally.

Initially subjects voided their bladders, mean arterial pressure was measured and 150 ml water was drunk. After each hour, mean arterial pressure was measured, urine volume was recorded on voiding, urine was sampled and 150 ml water was drunk. In the middle of each phase blood samples were taken for plasma separation. Urine and plasma samples were frozen for later analysis for creatinine, sodium and potassium.

For the middle 2-h phase subjects were fitted with a leak-free face mask connected to a non-rebreathing valve. Nitric oxide (1000 vpm in N_2) was mixed with air to an inspired concentration of 40 vpm. The mixture was delivered at 12 litres min^{-1} via reservoir bags and a reservoir tube. Inspired NO concentrations were monitored continuously with a chemiluminescence analyser.

On a separate day subjects returned for the control study, with the same plan, when air was breathed through the mask and apparatus during the middle phase.

Creatinine clearances and fractional and total sodium excretions were calculated for each 2-h phase using standard formulae. Urine volumes and mean arterial pressure were averaged for each of the 2-h phases.

Because of the large variation in urine volumes between subjects, volumes and calculated variables depending on them were corrected to relative values by dividing the values for a subject in a particular study period by the value obtained in the first control phase.

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Table 1 Results are mean (SEM). *P*-values are those returned from paired two-tailed '*t*'-tests. Italics indicates iNO. Bold indicates significance at 5%. FENa=Fractional sodium excretion, C=Control; Mid=Middle

	1st Control phase	**Middle phase**	**2nd Control phase**	**Between phases *P*-values**		
				1stC–Mid	**Mid–2ndC**	**1stC–2ndC**
Corrected urine volumes						
Experimental	1.00 (0.00)	*1.85 (0.22)*	0.65 (0.08)	**0.019**	**0.002**	**0.012**
Control	1.00 (0.00)	0.99 (0.32)	0.99 (0.28)	0.969	0.997	0.968
Corrected creatinine clearance						
Experimental	1.00 (0.00)	*1.06 (0.06)*	1.02 (0.14)	0.344	0.816	0.863
Control	1.00 (0.00)	0.87 (0.08)	0.94 (0.10)	0.184	0.669	0.608
Corrected FENa						
Experimental	1.00 (0.00)	*1.01 (0.11)*	0.55 (0.09)	0.942	**<0.001**	**0.008**
Control	1.00 (0.00)	0.68 (0.08)	0.68 (0.11)	**0.014**	0.952	**0.044**
Corrected sodium excretion						
Experimental	1.00 (0.00)	*0.92 (0.12)*	0.36 (0.05)	0.547	**0.008**	**<0.001**
Control	1.00 (0.00)	0.70 (0.13)	0.54 (0.10)	0.079	0.249	**0.011**
Mean arterial pressure (mm Hg)						
Experimental	91.1 (13.7)	*91.4 (11.4)*	91.7 (7.7)	0.941	0.941	0.936
Control	82.7 (11.1)	85.0 (10.3)	83.2 (8.7)	0.213	0.557	0.914

Variables were tested using a paired two-tailed '*t*'-test and differences were taken to be significant for *P*-values less than 0.05. No corrections were made for multiple comparisons.

The results are given in Table 1. Inhalation of nitric oxide increased urine volume which decreased after iNO was discontinued and was not seen in the control experiments. Absolute and fractional sodium excretion (FENa) remained unchanged during the nitric oxide phase, compared with a reduction in the control experiments. Creatinine clearance and arterial pressure did not change over time in both nitric oxide and control experiments.

Comment

These data suggest that in normal volunteers iNO is associated with a modest diuresis and a slight natriuresis. This is the first time that this has been reported in humans.

In the control experiment, urinary sodium and FENa decreased with time, whilst urine output and creatinine clearance remained stable. This is probably because the subjects were adjusting to the constraints of drinking 150 ml water each hour. A longer period of controlled fluid intake before the study would have been preferable.

With nitric oxide, a diuresis was evident through the iNO phase. Urinary sodium and FENa were maintained as iNO was inhaled. When compared to the progressive decrease observed in the control experiments, this suggests that iNO increases urinary sodium excretion and FENa. The absence of a change in creatinine clearance implies that there was no change in glomerular filtration rate (GFR) and, with no change in mean arterial blood pressure, the global haemodynamics appear unaltered. The diuresis thus arose because of the natriuresis, and so the effects of iNO appear to be tubular in nature, affecting sodium resorption along the nephron, rather than vascular or glomerular. These findings are subtly different from those reported by Troncy and colleagues in pigs which suggested iNO was inducing changes in glomerular blood flow.

iNO cannot leave the lung in its native state and it is therefore unlikely that NO is having a direct effect on the kidney. Its principle metabolite, nitrate, has been shown to be a diuretic,[4] but only at very high concentrations, far above those predicted for this study.

An alternative explanation would be for NO to be acting on the angiotensin converting enzyme (ACE) in the lungs. Small doses of angiotensin II that do not affect the arterial pressure have been shown to reduce total and fractional sodium excretion and urine volume without any change in GFR,[5] [6] and blockade of this system would result in the opposite effects, which is what we have observed here. So, if iNO was inhibiting ACE, angiotensin II levels would decrease to cause the observed results.

The nitric oxide donor sodium nitroprusside inhibits ACE *in vitro*,[7] as does shear stress to blood vessel walls,[8] both possibly through NO release. ACE itself has several cysteine residues whose thiol groups would be able to react with NO to modulate its activity.[9] This would support an ACE inhibition theory, but in the absence of better data and without angiotensin II measurements, this is highly speculative, and the effects seen could equally be related to changes in anti-diuretic hormone levels.

This study used quite high concentrations of iNO to induce a modest change in renal salt and water handling. Both the mechanism and clinical relevance remain to be determined.

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Can isoflurane mimic ischaemic preconditioning in isolated rat heart?

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Ischaemic preconditioning can protect the myocardium against ischaemic injury by opening of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel. Isoflurane is also thought to open this channel. The present investigation tested the hypothesis that pre-ischaemic treatment with isoflurane mimics ischaemic preconditioning (producing chemical preconditioning) and thereby protects the myocardium against ischaemic injury in an isolated rat heart model. Control hearts underwent 30 min of global no-flow ischaemia followed by 60 min of reperfusion. The hearts of the preconditioning group underwent two 5 min periods of no-flow ischaemia interspersed with 5 min of reperfusion before the sustained ischaemia. In three additional groups, hearts were subjected to 15 min of 1.5 minimal alveolar concentration (MAC) of isoflurane (ISO-1), 15 min 3 MAC (ISO-2) or 25 min 1.5 MAC (ISO-3) of isoflurane followed by 5 min washout before the global ischaemia. Left ventricular (LV) developed pressure and creatine kinase release were measured as variables of myocardial performance and cellular injury, respectively. Recovery of LV developed pressure was improved after ischaemic preconditioning [after 60 min reperfusion, mean 63 (SEM 6)% of baseline] compared with the control group [18 (4)% $P<0.01$] but not by isoflurane, independently of concentration or duration of administration [ISO-1, 17 (2)%, $P=0.99$ *vs* control; ISO-2, 12 (3)%, $P=0.64$; ISO-3, 4 (1)%, $P=0.06$]. Total creatine kinase release over 1 h of reperfusion was not significantly different between control [251 (36) U g^{-1} dry weight] and all isoflurane groups [ISO-1, 346 (24) U g^{-1}, $P=0.30$; ISO-2, 313 (33) U g^{-1}, $P=0.73$; ISO-3, 407 (40) U g^{-1}, $P=0.03$]. These results indicate that pre-ischaemic administration of isoflurane does not cause anaesthetic-induced preconditioning in the isolated rat heart.

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Brief ischaemic periods render the myocardium resistant to myocardial injury from subsequent ischaemic insults, a process called ischaemic preconditioning. The ATP-sensitive potassium (K_{ATP}) channel plays a major role in the mechanism of ischaemic preconditioning, and volatile anaesthetics have been shown to act on this channel.[1] In 1997, Cope and colleagues first demonstrated that pre-administration of some volatile anaesthetics followed by a washout period protects isolated rabbit myocardium against infarction and mimics the ischaemic preconditioning phenomenon (pharmacological or chemical preconditioning).[2] A similar protective effect was found *in vivo* in dogs[3] and rabbits.[4 5] In isolated rat hearts, volatile anaesthetics have been shown to be cardioprotective if administered before ischaemia without preischaemic washout.[6] However, without preischaemic washout a substantial anti-ischaemic effect of isoflurane cannot be excluded. We investigated whether chemical preconditioning-like effects of isoflurane can be induced in isolated rat hearts subjected to global ischaemia. We chose this model to prevent systemic effects of isoflurane and changes in collateral blood flow influencing ischaemic injury. To exclude anti-ischaemic effects, isoflurane was washed out 5 min before ischaemia.

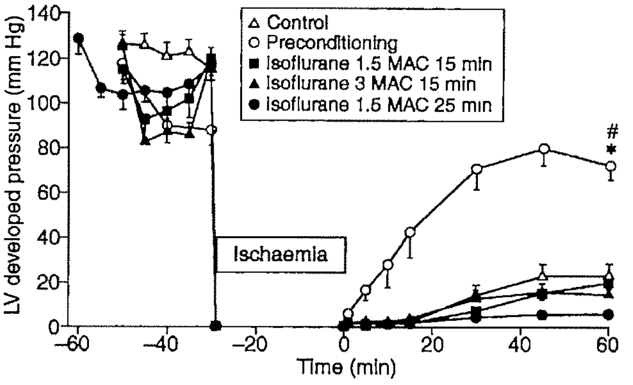

Fig 1 Effects of ischaemic preconditioning and isoflurane pretreatment on the recovery of left ventricular (LV) developed pressure in the reperfusion phase. LV developed pressure is plotted as a function of time. Data are mean (SEM), n=8 each group. *P<0.05, preconditioning *vs* control. #P<0.05, preconditioning *vs* all isoflurane groups.

Methods and results

The experiments were performed in accordance with the regulations of the German Animal Protection Law and local institutional regulations. The exact protocol has been described in detail previously.[7] In brief, hearts were excised from anaesthetized male Wistar rats (300–350 g body weight) and mounted in a Langendorff perfusion system. Retrograde perfusion via the aorta was initiated in constant pressure mode (80 mm Hg) with oxygenated modified Krebs–Henseleit buffer. The heart rate of the isovolumetric beating hearts was maintained at 375 beats min^{-1} by atrial pacing. A hollow-fibre oxygenator was integrated into the perfusion system and isoflurane was administered by an agent-specific vaporizer into the fresh gas supply of the oxygenator. A Datex infrared gas analyser controlled the delivered vapour concentration continuously. After preparation, a stabilization period of 20 min was allowed. The experimental programme consisted of three phases: intervention (20 or 30 min); global no-flow ischaemia (30 min); and reperfusion (60 min). Control hearts received no further treatment in the intervention phase. In a second group (PC), ischaemic preconditioning was induced by two 5 min periods of no-flow ischaemia, each followed by 5 min of reperfusion. The hearts of the isoflurane groups received 15 min 1.5 minimal alveolar concentration (MAC) (ISO-1), 15 min 3 MAC (ISO-2) or 25 min 1.5 MAC of isoflurane (ISO-3), followed by 5 min washout before global ischaemia (1 MAC=2.3% Vol in the rat). Left ventricular (LV) developed pressure [LV peak systolic pressure minus LV end-diastolic pressure (LVEDP)], LVEDP, oxygen consumption and creatine kinase release were measured as variables of myocardial performance and cellular injury, respectively. Data are expressed as mean (SEM). Statistical analysis was performed by two-way analysis of variance (ANOVA) for time and treatment effects. If an overall significant difference was found, comparison was made for each time using one-way ANOVA followed by the Tukey–Kramer post test (between groups) or Dunnett's post test (*vs* baseline) when appropriate. P<0.05 was regarded as significant.

A total of 40 hearts were included in the statistical analysis (five groups, n=8 each). Baseline values were similar in all groups. Postischaemic function of control hearts was markedly depressed and LV developed pressure recovered to only 18 (4)% of baseline values (P<0.01) after 60 min reperfusion (Fig. 1). In the PC group, the two 5 min periods of ischaemia had almost no influence on haemodynamic variables after 5 min of washout, except for LV developed pressure which decreased from 117 (7) mmHg to 88 (7) mmHg (P=0.01 PC *vs* baseline). The preconditioning protocol resulted in better preservation of myocardial performance after 30 min of global ischaemia in comparison with control hearts. LV developed pressure finally reached 63 (6)% of the baseline value (P<0.01 *vs* control). Isoflurane could not mimic the myocardial protection produced by preconditioning. LV developed pressure recovered to 17 (2)% of baseline (ISO-1, P=0.98 *vs* control), 12 (3)% (ISO-2, P=0.64 *vs* control) and 4 (1)% (ISO-3, P=0.06 *vs* control), similar to the control hearts and significantly lower in comparison with PC (P<0.01 *vs* all isoflurane groups). LVEDP increased in control hearts during ischaemia to a peak value of 36 (4) mm Hg after 25 min, indicating myocardial contracture (Table 1). During early reperfusion, there was a further increase in LVEDP, which reached a maximum of 100 (6) mm Hg (P<0.01 *vs* baseline) at 5 min of reperfusion (reperfusion contracture). At the end of the experiment, LVEDP in control hearts was still elevated [60 (7) mm Hg, P<0.01 *vs* baseline]. Ischaemic preconditioning

Table 1 LVEDP and metabolic measurements. Variables are mean (SEM), $n=8$ for each group. LVEDP=ventricular end-diastolic pressure. Creatine kinase release (CKR) during 60 min of reperfusion and oxygen consumption at the end of the reperfusion period are expressed per g dry weight. *$P<0.05$ *vs* control and preconditioning; **$P<0.05$ *vs* all other groups

	LVEDP (mm Hg)			**CKR ($U\ g^{-1}$)**	**Oxygen consumption ($\mu l\ min^{-1}\ g^{-1}$)**
	Baseline	**Ischaemia**	**Reperfusion**		
Control	10 (1)	36 (4)	60 (7)**	251 (36)	439 (53)**
Preconditioning	8 (2)	23 (6)	22 (7)	247 (39)	770 (92)
ISO-1	13 (1)	42 (5)	60 (6)**	346 (24)	418 (55)**
ISO-2	10 (1)	54 (4)**	65 (6)**	313 (33)	283 (81)**
ISO-3	10 (1)	49 (5)**	78 (6)**	407 (40)*	336 (81)**

reduced the degree of myocardial contracture in the ischaemic period [maximum LVEDP 23 (6) mm Hg] and in the reperfusion phase. After 60 min of reperfusion, LVEDP was only slightly elevated in the PC group [22 (7) mm Hg, $P=0.73$ *vs* baseline] and was significantly lower than the control. The extent of myocardial contracture was not affected by isoflurane administration. LVEDP increased to 60 (6) (ISO-1, $P=1.00$ *vs* control), 65 (4) (ISO-2, $P=0.99$ *vs* control) and 78 (5) mm Hg (ISO-3, $P=0.25$ *vs* control) at the end of reperfusion, significantly higher than in preconditioned hearts ($P<0.01$ *vs* all isoflurane groups). Oxygen consumption during baseline was 1047 (99) $\mu l\ min^{-1}\ g^{-1}$ dry weight, and was similar in all groups. Oxygen consumption was reduced after the reperfusion period in control hearts to 439 (53) $\mu l\ min^{-1}\ g^{-1}$. Preconditioning led to greater oxygen consumption at the end of reperfusion (Table 1), indicating a greater amount of viable tissue in this group. In contrast, oxygen consumption in all isoflurane groups was similar to that in the control group and lower than that in the PC group (Table 1). Isoflurane did not reduce the amount of cell necrosis, as shown by creatine kinase release as an indicator of cellular injury. Cumulative creatine kinase release after 1 h of reperfusion was 251 (36) $U\ g^{-1}$ dry weight in control hearts. Creatine kinase release was not reduced by pre-ischaemic administration of isoflurane (Table 1).

Comment

The results of the present study demonstrate that isoflurane, regardless of the concentration used and the duration of administration, does not produce pharmacological preconditioning in isolated rat hearts. These findings are in contrast to four recent studies, which can be summarized as follows. (i) Isoflurane mimicked ischaemic preconditioning in a canine model *in vivo* and in rabbit models *in vivo* and *in vitro* with regional ischaemia and reperfusion.[2, 3] (ii) Cardioprotection was independent of the systemic effects of the volatile anaesthetic (*in vitro* model) and of increases in collateral blood flow (rabbit model with almost no coronary collateralization).[2, 5] (iii) The effect could be observed with low (0.6 MAC) and high (2 MAC) concentrations of isoflurane, short (5 min) and long (65 min) durations of administration and different time intervals between isoflurane administration and prolonged ischaemia (5–30 min).[3–5] (iv) Cardioprotection by isoflurane could be abolished by preadministration of glyburide, a specific blocker of the K_{ATP} channel.[3, 5] These results demonstrate a preconditioning-like effect of isoflurane (pharmacological preconditioning) in different experimental models and with different experimental protocols. However, these effects could not be confirmed in isolated rat hearts. Besides differences in models (regional *vs* global ischaemia) and protocols (duration of isoflurane administration, pre-ischaemic washout), it is likely that pharmacological preconditioning by isoflurane is species-dependent and the isolated rat heart is not a suitable model for the study of anaesthetic-induced preconditioning. Species differences make it difficult to transfer results of previous experimental studies to possible effects on the human myocardium.

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Post-operative recovery: day surgery patients' preferences

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Due to the growing importance of quality assurance and cost containment in healthcare, eliciting patients' preferences for post-operative outcomes may be a more economical and reliable method of assessing quality. Three hundred and fifty-five day surgery patients completed a pre-operative written questionnaire to identify patients' preferences for avoiding 10 particular post-operative symptoms: pain, nausea, vomiting, disorientation, shivering, sore throat, drowsiness, gagging on the tracheal tube, thirst and a normal outcome. The two scoring methods used to evaluate preferences were priority ranking and relative value scores. The effects of age, gender, previous health status, type of surgery and previous experience of anaesthesia on patients' preferences were also examined. Avoiding post-operative pain, gagging on the tracheal tube and nausea and vomiting are major priorities for day-case patients. Anaesthetists should take patients' preferences into consideration when developing guidelines and planning anaesthetic care.

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Recent advances in surgical practice combined with the use of 'fast-tracking' anaesthetic techniques have led to a dramatic increase in the number of patients discharged on the same day as surgery. Although 70–80% of all elective cases in North America are now performed as day surgery, there has been little critical evaluation of the outcome of the service.

Obtaining patient perceptions may be more economical and reliable than traditional methods of assessing quality.[1] By identifying what patients want, we can tailor guidelines for anaesthetic care to suit patients' needs and improve the quality of care provided. Preference-based guidelines are more likely to meet criteria for high quality guidelines than those developed without considering patients' preferences.[2]

To our knowledge only one group of investigators, Macario and colleagues,[3] has attempted to identify and measure patients' preferences for avoiding adverse outcomes in the post-operative period. Their study population included in-patients (63) and day-case patients (38) and was not powered to determine whether physiological characteristics, variables or type of surgery affected patients' preferences.

The aim of this study was to use patient and anaesthetist interviews to generate items for inclusion in a questionnaire, identifying day-case patients' preferences for avoiding post-operative symptoms. The secondary aims were to use this questionnaire to measure patients' preferences for the post-operative recovery and to validate Macario's findings using a larger sample size. The effect of patient age, gender, American Society of Anesthesiologists (ASA) status, type of surgery or a history of previous anaesthesia on patients' responses was also assessed.

Methods and results

Institutional Ethics Committee approval was obtained and all the patients gave informed written consent. Qualitative in-depth interviews of 22 unpremedicated adult day-case ASA I and II patients and 15 anaesthetists were conducted. Items generated from patient and anaesthetist surveys were used to devise the final questionnaire, ensuring face and content validity.

The final questionnaire was administered to 400 consecutive unpremedicated adult ASA I and II patients in the day surgery unit, about to undergo short (1–2 h) day-case surgical procedures under general anaesthesia or regional anaesthesia with sedation. Physical characteristics including the patients' age, sex, ASA status, type of surgery and previous surgery were recorded.

Two different methods were used to elicit patients' preferences for avoiding 10 different post-operative outcomes. First, patients were asked to rank their preferences

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Table 1 Description of post-operative symptoms

Symptom	Description
Pain	You wake up moaning or writhing and need extra painkillers
Nausea	You feel queasy with a strong desire to vomit
Vomiting	You are retching and bringing up liquid or solids
Disorientation	After waking up, you do not know your surroundings
Shivering	You feel cold and have shaking of your body
Sore throat	Your throat is painful and it may hurt when you try to swallow
Normal	You are awake, alert, comfortable and aware of your surroundings
Drowsiness	You feel very sleepy and tired and do not want to get out of bed
Gagging on the endotracheal tube	You have a choking sensation due to the presence of a small tube in your throat to assist your breathing
Thirst	Your mouth feels dry and you have a strong desire to drink

between 1 and 10 for avoiding a particular set of post-operative symptoms from 1 'least upsetting outcome' to 10 'most upsetting outcome'. Each symptom was clearly defined, for example, nausea as 'you feel queasy with a strong desire to vomit' (Table 1). Normal was included and defined as 'you are awake, alert, comfortable and aware of your surroundings'. They were instructed not to use the same score for more than one outcome. Second, preferences were elicited for the same set of outcomes using relative value scores. Patients were asked to imagine a situation where they were given $100 to spend so that they could reduce the likelihood of particular symptoms occurring in the immediate post-operative period. The more money they spent on a particular symptom the less likely it was to occur, but the total amount had to equal $100. The dollar allocations assigned to a particular outcome were used to determine the relative value of each outcome.

Using the same methods as Macario and colleagues,[3] the internal validity of the questionnaire was tested by analysis of the correlation between the ranking data and the relative value data using Spearman-Rank correlation. Symptoms within the ranking scale and within the relative value scoring scale were compared using non-parametric testing (Kruskal-Wallis). A P value of <0.05 was considered statistically significant.

Three hundred and fifty-five day-case ASA I and II patients completed the questionnaire. The majority of patients were female (62%) and ASA class I (77%). Most patients were scheduled to undergo orthopaedic (46%), gynaecological (31%) or ophthalmic (17%) procedures and 79% of patients had undergone surgery and anaesthesia previously. The age range was 15–80 yr, average 39 yr.

Using patient rank scores to measure patients' perceptions of outcomes, pain, nausea and vomiting and gagging on the tracheal tube were considered to be most upsetting followed by disorientation, sore throat, shivering, drowsiness and thirst. Using dollar allocations to measure the relative value of avoiding each symptom, pain was assigned the highest relative value score, followed by gagging on the tracheal tube, vomiting and nausea (Table 2). The correlation coefficients between median rank score and relative value score were significant for all symptoms ($P<0.05$). These findings are consistent with those of Macario's smaller study of 101 patients which used 'anaesthesia outcomes' formulated by a group of experts with no patient input.[3]

Table 2 Results of priority ranking and relative value scores

Outcome	Rank (median (range))	Relative value score (mean (SD))
Pain	9 (1–10)	26.1 (19)
Gagging on tracheal tube	8 (1–10)	16.9 (16)
Vomiting	8 (1–10)	15.6 (15)
Nausea	8 (1–10)	11.6 (11)
Disorientation	6 (1–10)	6.6 (9)
Sore throat	5 (1–10)	6.1 (8)
Shivering	5 (1–10)	5.1 (6)
Drowsiness	4 (1–10)	5.3 (8)
Thirst	4 (1–10)	4.9 (9)
Normality	1 (1–4)	0.5 (2)

Comment

To our knowledge, this study is the first to examine the effects of age, gender, previous health status (based on ASA classification), type of surgery and previous experience of anaesthesia on patients' preferences for day surgery. Comparing patient preferences in older (50+ yr) vs. younger age groups, the older patients attributed less importance to adverse outcomes than the young, ranking pain, nausea and vomiting lower ($P<0.05$). This finding is consistent with previous work that showed older patients were generally more satisfied with care than younger patients.[4]

There were no significant differences in scores among the other subgroups of patients. Regarding sex differences, other studies reported that women expressed more fears and different concerns about anaesthesia than men.[4 5] This study found no difference in patient preferences between men (38%) and women (62%). ASA status and type of surgery, similarly, had no significant effect on patient preferences.

There were no significant differences in preferences of those who had never experienced anaesthesia (21%) and those who had (79%), in keeping with the results of Klafta and colleagues.[5] This finding is contrary to the normal expectation that previous good experiences may allay anxiety.

Measurement of patient satisfaction with anaesthetic care is inherently difficult as it depends on a multitude of factors. Patients may just be expressing global satisfaction with hospital care and surgery, relief that they have survived intact or may be unwilling to criticize the system for fear of jeopardizing their future care. Patients tend not to recall anaesthetic complications when questioned generally (10%); however, most of the same group (80%) will identify at least one complication when shown a list of specific symptoms.[6] Hence single global ratings of satisfaction with anaesthesia, although uniformly high (>80%), are insensitive to detecting deficient areas of care. The use of psychometric methods, which quantitatively assess the desirability of health states or outcomes from the patient's perspective, may be more useful.

Patients' preferences in this study highlight areas for clinical improvement. Incidences of minor morbidity, such as pain and post-operative nausea and vomiting, have not changed significantly over the last 25 yr despite improvements in anaesthetic drugs and techniques. Post-operative pain should be aggressively managed, both in the recovery room and following discharge. The ongoing debate of the relative benefits of prophylactic vs. rescue antiemetic therapy should take each patient's preference for post-operative recovery into consideration.

Although efforts to minimize patients' discomfort as a result of gagging on the tracheal tube should be undertaken, patient safety must not be compromised. The description of 'a choking sensation due to the presence of a small tube in your throat to assist your breathing' may have influenced patients to assign a high score to this outcome. Anaesthetists should be encouraged to explain to their patients preoperatively that some outcomes may be inevitable if safety is to be ensured, but reassure them that they are temporary and short-lived.

Further work should assess patients' perceptions of quality of care including, not only clinical outcome, patient's expectations and satisfaction, but also other aspects such as the care environment, for example hospital facilities and of the interpersonal skills of the staff. Also, processes that enable the care to be delivered should be examined, for example technical aspects, operating room turnover and discharge procedures.[7 8]

In this growing era of quality assurance and cost containment, clinicians should take patients' preferences into consideration when developing guidelines and planning anaesthesia care.

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Attenuation of haemodynamic responses to tracheal intubation by the StyletScope

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Tracheal intubation often causes a haemodynamic response probably generated by direct laryngoscopy. The StyletScope is a new intubation device that does not require direct laryngoscopy. We prospectively measured haemodynamic changes after tracheal intubation using the StyletScope. The increase of heart rate was less during tracheal intubation with the StyletScope when compared with the Macintosh laryngoscope.

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Keywords: airway; equipment, layngoscopes fibreoptics; cardiovascular system, responses; complications, intubation tracheal

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The StyletScope (NihonKohden Corp., Tokyo, Japan) is a new fiberoptic intubation device with a lightweight stylet, manoeuverability of the distal tip, a built-in light source and does not need time to set up or external video systems.[1] It allows successful tracheal intubation in a short time.[2] Direct larynoscopy for tracheal intubation frequently causes haemodynamic responses.[3] As intubation with the StyletScope does not require direct laryngoscopy, haemodynamic responses to tracheal intubation may be less. We compared the haemodynamic responses to tracheal intubation using the StyletScope or the Macintosh laryngoscope.

Methods and results

After approval from the ethics committee of our institute and with informed consent from each patient, we studied 24 consecutive patients. Exclusion criteria were ages less than 20 or greater than 85 yr, American Society of Anesthesiologists physical status IV, and the known risks of regurgitation.

At the pre-operative visit the difficulty of the airway was graded by the Mallampati test modified by Samsoon and Young.[4] All patients were pre-medicated with atropine 0.01 mg kg^{-1} and hydroxyzine 0.5 mg kg^{-1} i.m. Electrocardiography (ECG), capnography, pulse oximetry, and non-invasive arterial pressure monitoring were applied. After pre-oxygenation with 100% oxygen, general anaesthesia was induced with fentanyl 2 $\mu g\ kg^{-1}$, propofol 1 mg kg^{-1} followed by continuous infusion at 10 mg $kg^{-1}\ h^{-1}$, and vecuronium 0.15 mg kg^{-1}. Patients were then randomly allocated to one of two groups. Patients in group L (n=11) underwent tracheal intubation using the Macintosh laryngoscope (blade No. 3). Patients in group S (n=13) underwent tracheal intubation using the StyletScope alone. The intubation procedure using the StyletScope alone has been described previously.[2] Intubation was started 5 min after starting the infusion of propofol, with the patient's head and neck in the sniffing position. The infusion rate of propofol was not changed until 5 min after tracheal intubation. All intubation procedures were carried out by the same anaesthesiologist (T.K.) after familiarization with the StyletScope.

Ethical considerations did not allow the use of any invasive monitoring. Non-invasive arterial pressure and heart rate (HR) were recorded. As several studies have found that maximum haemodynamic responses occur about 1 min after tracheal intubation,[3 5–7] we calculated the per cent changes in haemodynamic variables from before intubation to 1 min after the completion of intubation. We also recorded the time required for tracheal intubation, beginning at the moment of inserting the Macintosh laryngoscope (group L) or a tracheal tube with the StyletScope (group S) into the mouth until a standard stylet (group L) or the StyletScope (group S) was removed.

Data are shown as means (SEM). Paired and unpaired t-tests and chi-squared tests were used to compare data.

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Table 1 Characteristics of patients and changes in haemodynamics. Data are shown as means (SEM). *$P<0.05$, paired t-test, compared with pre-induction value of the same group. †$P<0.05$, unpaired t-test, compared with the per cent increase in the same haemodynamic parameter of group L. ASA-PS, American Society of Anesthesiologists physical status. SBP, systolic arterial pressure; DBP, diastolic arterial pressure. HR, heart rate. Per cent increase, per cent increase in each haemodynamic parameter from pre-intubation period to post-intubation

Patient characteristics **Group**	**Sex (M/F)**	**Age (yr)**	**Height (cm)**	**Weight (kg)**	**ASA-PS (I/II/III)**	**Patients with hypertension**	**Class of Mallampati (I/II/III/IV)**
L (n=11)	4/7	54 (4)	159 (2)	55 (3)	7/2/2	4/11	8/3/0/0
S (n=13)	5/8	55 (4)	160 (2)	57 (4)	7/5/1	3/13	8/4/1/0

Changes in haemodynamics	**Group**	**Pre-induction**	**Pre-intubation**	**Post-intubation**	**Per cent increase (%)**
HR (beat min^{-1})	L	74 (4)	68 (4)*	91 (5)*	34 (5)
	S	74 (3)	66 (3)*	73 (3)	11 (4)†
SBP (mm Hg)	L	139 (10)	101 (8)*	135 (13)	34 (7)
	S	129 (6)	100 (3)*	121 (6)	21 (5)
DBP (mm Hg)	L	80 (4)	58 (5)*	78 (9)	35 (7)
	S	74 (4)	58 (3)*	69 (6)	20 (7)

Statistical analyses were performed using StatView for Windows version 5.0. A P value less than 0.05 was considered to be statistically significant.

The groups were similar in respect of all characteristics. The laryngeal structures of patients in group L were graded according to Cormack and Lehane,[8] at direct laryngoscopy. All patients in group L were graded as grade I or II.

As shown in Table 1, after induction of general anaesthesia, all haemodynamic measurements decreased significantly from baseline values in both groups (paired t-test). After intubation, only the HR in group L was significantly greater than the baseline value (paired t-test), but other haemodynamic variables returned toward baseline values in both groups. The increase in HR was less in group S than group L (unpaired t-test). The increases in systolic and diastolic arterial pressure tended to be less in group S than group L, but there were no significant differences (unpaired t-test).

No ECG abnormalities were observed. Sp_{O_2} remained above 99% in all patients. Success rates of tracheal intubation at the first attempt were 11/11 and 12/13 in group L and group S, respectively. The failed case in group S was because of mucus on the distal tip of the StyletScope, and was intubated successfully at the second attempt. Mean times (SEM) required for tracheal intubation were 21 (2) and 20 (3) s in group L and group S, respectively. There were no significant differences between the two groups (unpaired t-test). No adverse effects were associated with tracheal intubation were observed, but on the first postoperative day, slight sore throat was observed in 6/11 and 2/13 patients of group L and group S, respectively. The incidence of sore throat was significantly lower in group S than group L (chi-squared test).

Comment

We found that the StyletScope reduced the increase of HR during tracheal intubation. Direct laryngoscopy causes haemodynamic responses to tracheal intubation.[3] Placement of the tracheal tube through the vocal cords and inflation of a cuff causes little greater stimulus.[3] The StyletScope eliminates direct laryngoscopy. We consider that this reduces haemodynamic responses. Although these responses are usually transient and uneventful, they could be harmful in some patients with cardiovascular or cerebrovascular diseases. In patients with ischaemic heart disease, strict control of haemodynamics is required, as ischaemic events are associated with a greater rate of perioperative myocardial infarction.[9] HR is a major determinant of myocardial oxygen balance.[10] Although this study included no patients with ischaemic heart disease, our results suggest that the StyletScope is a good choice as an intubation device for such patients.

The reduced response to tracheal intubation using the StyletScope was accompanied by a significantly smaller incidence of sore throat. This is probably for the same reason that the stimuli from direct laryngoscopy are eliminated. Compared with the Macintosh laryngoscope, some fiberoptic devices need more time for intubation, but we found no significant difference in the time required for intubation between the two groups. The success rate for tracheal intubation using the StyletScope was high enough for practical use, confirming the efficiency of the StyletScope we have reported previously.[1 2]

In conclusion, the StyletScope causes less haemodynamic response to tracheal intubation. Because of this, the StyletScope may be a valuble intubation device especially for patients in whom haemodynamics disturbances should be limited.

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BJA

CASE REPORTS

Unexplained acute severe methaemoglobinaemia in a young adult

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This report describes the case of an otherwise healthy young adult female, who presented with a 12-h history of progressive bluish discolouration of lips and limbs. She denied ingesting or inhaling any drug or substance. A high Pa_{O_2} in the presence of 'cyanosis' and 'dark blood' led to suspicion of methaemoglobinaemia. Co-oximetry revealed the methaemoglobin level to be 47%. A urinary screen for drugs of abuse was negative and blood methaemoglobin reductase activity was within the normal range. The aetiology was traced to dapsone detected in the urine by gas chromatography/mass spectrometry. The therapeutic and diagnostic approach in such patients is discussed.

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Keywords: pharmacology, dapsone; complications, methaemoglobinaemia

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Acute severe methaemoglobinaemia is an uncommon but potentially treatable disorder in which patients can present with dramatic signs and symptoms. Usually there is a history of some precipitating factor such as accidental or intentional ingestion of a drug or inhalation of certain substances. It is also well known that administration of certain medications can precipitate methaemoglobin (MetHb) formation in cases of overdose or even in normal doses if the patient is susceptible. We report the case of a young woman who presented with severe methaemoglobinaemia without any positive history.

Case report

A 29-yr-old female was referred by a general practitioner with a 12-h history of progressive bluish discoloration of limbs and lips, shortness of breath, several episodes of vomiting and pain in the anterior chest. She had consumed moderate quantities of alcohol the previous night at a pub. Apart from a history of taking two tablets of acetaminophen during the previous 24 h, she denied ingesting or inhaling any other drug. There was no past history suggestive of similar episodes or other illness, drug abuse, deep vein thrombosis or pulmonary embolism. She was a non-smoker. She was fully oriented, afebrile, anxious and had generalized cyanosis. The pulse rate was 145 beats min^{-1} and regular, the arterial pressure was 122/88 mm Hg and the jugular venous pressure was not raised. The respiratory rate was 35 bpm but the chest was clear to auscultation with normal heart sounds. Electrocardiogram, chest x-ray, full blood count, coagulation variables and serum biochemistry were normal. Arterial blood gas on 80% oxygen by mask showed pH 7.46, Pa_{O_2} 25 kPa, Pa_{CO_2} 2.7 kPa, HCO_3 15.3 mmol $litre^{-1}$, base excess—10 mmol $litre^{-1}$ and oxygen saturation of 98%. The pulse oximeter showed a haemoglobin saturation of 65% with a good pulse waveform. Blood alcohol, acetaminophen and salicylate were undetectable. Pulmonary embolism was suspected and heparin 10 000 units was given i.v. A computed tomography scan of the thorax to exclude pulmonary embolism and aortic dissection was normal. The patient was transferred to the intensive care unit and administered continuous positive airway pressure support by mask on 100% oxygen. During a repeat arterial blood gas sampling, it was noticed that the blood was dark coloured and the results showed a pH 7.46, Po_2 70 kPa, Pco_2 2 kPa, BE—10 mmol $litre^{-1}$, and oxygen saturation of 98%.

In view of the high Pa_{O_2} and the dark colour of the arterial blood, methaemoglobinaemia was suspected. Co-oximetry revealed MetHb levels to be 47%. Fifty milligrams of 1% methylene blue was given i.v. with 1 g of oral vitamin C. The MetHb levels ranged from 13.8 to 31% over the next 72 h and the patient required five additional doses of methylene blue 50 mg. In retrospect, there was no history of ingestion of fava beans or contact with aniline dyes. Red cell glucose-6-phosphate dehydrogenase levels were normal. A urinary

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screen for opiates, amphetamines, benzodiazepines, cocaine metabolites, barbiturates, cannabinoids and lysergic acid diethylamide was negative. Blood MetHb reductase activity was within the healthy population reference range. The patient was discharged to the ward on day 4 when the MetHb levels fell below 15% and she made an uneventful recovery. A basic extract of the urinary sample taken on day 3 was analysed by gas chromatography/mass spectrometry (Hewlett Packard 6890 series Gas Chromatograph and 5973 Mass Selective Detector). A peak with a retention time of 15.04 min under our operating conditions, gave a 97% match with the Pfleger MS Drug Spectral Library for dapsone. A smaller peak with a retention time of 10.81 min gave a 90% match with the Pfleger library for benzylbutylpthalate. This result suggested prior ingestion of dapsone although the patient denied that possibility. There was no history suggestive of either the patient or her immediate relatives taking dapsone for therapeutic reasons. There was no evidence of haemolysis or anaemia.

Discussion

Methaemoglobinaemia is a condition in which an abnormal proportion of the iron in the haem moiety of haemoglobin is oxidized to the ferric state leading to impaired oxygen transport and 'anaemic hypoxia'. The initial presentation of methaemoglobinaemia may cause diagnostic confusion because of the 'low' oxygen saturation on the pulse oximeter in favour of the 'cyanosis'. Standard pulse oximeters give spuriously low readings in the presence of excess methaemoglobin. The pulse waveform is not disturbed as long as peripheral circulation is maintained. All this can lead to performance of unnecessary investigations and administration of certain potentially hazardous drugs. In our patient, the results of the first arterial blood gas done in the ward to assess the severity of hypoxaemia might have aroused suspicion but it was felt that the patient had clinically deteriorated (become more blue) in the interval between arterial puncture and the availability of the results. The 'normal' oxygen saturation on the blood gas analysis and tachycardia along with tachypnoea diverted the attention to other possibilities. Most arterial blood gas analysers calculate the oxygen saturation based on the Pa_{O_2} and hence give 'false high' values in such cases. The dark coloured blood with a high Pa_{O_2} from the second blood gas analysis in the intensive care unit led to the suspicion of methaemoglobinaemia.

Clinical features of methaemoglobinaemia depend on the MetHb levels in blood. The discolouration of blood and appearance of cyanosis manifests when the MetHb levels reach 15–20%. Levels between 20–45% are associated with dyspnoea, lethargy, dizziness and headaches. MetHb levels above 45% are usually associated with impaired consciousness and levels above 55% can cause seizures, coma and cardiac arrhythmias. Although the lethal concentration for adults is considered to be >70%, survival has been reported with levels as high as 83%.[1]

Methaemoglobinaemia can be caused either by a genetic defect in red cell metabolism or haemoglobin structure, or acquired by a variety of drugs and toxins. About forty substances have been implicated in causing this condition, the most prominent being dapsone, nitrates, prilocaine, antimalarials, sulphonamides and dyes. Domestic causes of acquired methaemoglobinaemia include ingestion of food and water high in nitrites and nitrates,[2] inhalation of room odourizers containing butyl nitrite, exposure to aniline dyes in dyed blankets, laundry markings, freshly dyed shoes, red wax crayons[3] and cleaning solution.[4] Most contain some form of nitrates. Methylene blue when given in doses of over 15 mg kg^{-1} can itself cause methaemoglobinaemia and haemolysis but the MetHb levels rarely exceed 8%.[5] One important differential diagnosis for methaemoglobinaemia is sulphaemoglobinaemia. Sulphaemoglobin can be detected by most standard co-oximeters. Once the diagnosis is established, all the possible causes of methaemoglobinaemia should be considered. Information from the patient's relatives may prove beneficial. Apart from the potential-offending agents, a search should be made for other substances of abuse, which can be co-ingested. Where appropriate, methaemoglobin reductase activity should be measured.

There have been a number of reports of methaemoglobinaemia because of dapsone.[5–8] In all the cases, there was a history of ingestion of the drug. Dapsone is almost completely absorbed from the gastrointestinal tract and undergoes entero-hepatic circulation.[6] The plasma elimination half-life of dapsone is reported to vary from 10 to 80 h and is dose dependent. Renal excretion of unchanged dapsone is limited to approximately 20% of the administered dose. Dapsone is used in the treatment of leprosy and certain skin conditions. This patient did not have any skin lesions. The urine sample results taken on day 3 and the long duration of the methaemoglobinaemia in spite of treatment with methylene blue favoured dapsone as the offending agent. As for the source of dapsone, it is possible that the patient was given dapsone under the guise of 'ecstasy' tablets along with the alcohol. Benzyl butylphthalate is one of the plasticizers present widely in various household substances. Although there is a risk of chronic toxicity, acute toxicity is not known in humans.

This report describes a case of severe methaemoglobaemia without any positive history. The aetiology was traced to the possible ingestion of dapsone, which was detected in the urine by gas chromatography/mass spectrometry.

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Total spinal anaesthesia in association with insertion of a paravertebral catheter

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An association between intercostal nerve block and the development of a total spinal is rare. Usually, subarachnoid injection is considered to have followed intraneural placement or inadvertent entrance into a dural cuff extending beyond an intervertebral foramen. We report a patient that followed injection of local anaesthetic into a paravertebral catheter sited at surgery in the thoracic paravertebral space of a patient undergoing thoracotomy. This was a life-threatening event that occurred on two occasions before the definitive diagnosis was made. It is considered likely that the paravertebral catheter entered an intervertebral foramen and the tip perforated the dura.

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The thoracic paravertebral space is triangular in cross-section and bound by the pleura, vertebral bodies and lateral processes of the vertebrae and contiguous ligaments. It has proved a useful site for the administration of local anaesthetics and catheter insertion as the contents include the proximal tracts of intercostal nerves and the sympathetic chain.[1] The technique of placing catheters during thoracic surgery is proving increasingly popular and generally should be without complication if chest drains are present and low concentrations of local anaesthetic are used.[2]

Case report

A 62-yr-old woman was scheduled for right upper lobectomy for a bronchogenic carcinoma. This had been an incidental finding during a recent hospital admission for an infero-posterior myocardial infarction, from which she had made a good recovery. Other medical history of note was a right nephrectomy for tuberculosis 39 yr previously.

She was unpremedicated before surgery and anaesthesia was induced with remifentanil, thiopentone and vecuronium. She was ventilated via a medium left-sided Robertshaw tube and anaesthesia was maintained with isoflurane and a remifentanil infusion. Pre-operative paravertebral blocks at T4 and T7 were performed using 'one shot' percutaneous techniques, and a total of 18 ml of 0.5% bupivacaine with 1 in 200 000 adrenaline.

After an uncomplicated resection, a paravertebral catheter was inserted via a separate skin puncture and the catheter threaded under direct vision extrapleurally using

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forceps, with no apparent problem. Chest drains were sited, and the chest wall was closed. At the end of surgery, 0.25% plain bupivacaine 20 ml was injected through the paravertebral catheter. Morphine 5 mg i.v. was administered, the remifentanil infusion stopped and neuromuscular block reversed.

As the patient was being transferred back onto her bed it was noted that her systolic blood pressure had decreased to 50 mm Hg. This hypotension responded to metaraminol (3 mg in 1 mg aliquots). Her trachea was still intubated and haemoglobin oxygen saturations were maintained at 98% with manual ventilation with 100% oxygen. Clinical examination excluded pneumothorax or acute haemorrhage as a cause of the hypotension and, as she was still making no respiratory effort after a further 20 min, arterial blood gases were checked and signs of opioid narcosis sought. Although her pupils were widely dilated and poorly reactive at this time, blood gases showed a Pa_{CO_2} of 11 kPa. Therefore, it was thought likely that this was the cause (i.e. carbon dioxide retention) of her persistent unresponsiveness and pupillary signs. Her double lumen tube was changed for an oral tracheal tube, with no cardiovascular response to intubation and no need for further drugs to be given. She was ventilated for another 30 min after which she woke up and began to breathe. Her pupils were now normal in size and reactivity and she was transferred to a high dependency unit. She had no recall of these events.

In view of her complicated recovery, the usual bupivacaine paravertebral infusion was not commenced immediately post-operatively. Two hours later, she complained of pain at her thoracotomy site. A 10 ml bolus of 0.25% plain bupivacaine was administered by an anaesthetist. Her pain relief was immediate which alerted the anaesthetist to the possibility of subarachnoid injection. Shortly after, she became apnoeic, unresponsive, hypotensive and developed fixed dilated pupils. Intubation and resuscitation were immediate. Her hypotension responded to a colloid bolus and adrenaline 100 µg i.v. She was given midazolam 10 mg and transferred to ITU.

Over the next 2 h she woke up and began to breathe again. Lower limb weakness persisted for a further hour, but by the following morning she had no residual neurological deficit of subarachnoid injection or adverse effects from dural puncture. Recovery to hospital discharge was unremarkable apart from a brief episode of supraventricular tachycardia, which was not felt to be related to her anaesthetic complications.

Discussion

The immediate response to the second critical incident, after resuscitation, was to remove the paravertebral catheter. Serum bupivacaine concentration measured on arrival in ITU was 0.72 mg litre^{-1}, which is well below toxic concentrations or those associated normally with regional block. The clinical presentation at the second incident was classical for a 'total spinal'. However, this is an unusual complication of paravertebral block and would be difficult to diagnose in an unconscious patient immediately after surgery.

It is known that extradural spread is common with paravertebral block, because of the proximity of the extradural space to the injection site,[1] but the clinical relevance of this association in acute pain relief is still a matter of debate. The volumes of drug administered and speed of onset of block makes it unlikely that these events were a result of what has been described as a massive extradural injection.[3]

Lonnqvist and colleagues,[4] looked at clinical problems associated with percutaneous paravertebral block in 367 patients. Thoracic surgery patients were included in their casemix, but no patient showed signs of subarachnoid injection. There have been some reports of postural headache after percutaneous paravertebral injection but without CSF aspiration, and there is a report of a series in which a medial approach to the paravertebral space resulted in a dural puncture incidence rate of less than 1.0%.[5] In our patient, there had been no attempts at extradural injection and the pre-operative paravertebral injection had been via a relatively lateral approach, so it is thought unlikely that the patient had sustained any dural trauma explaining the spread of local anaesthetic from the paravertebral space, through an intervertebral foramen into the subarachnoid space.

There have been a few reports of subarachnoid spread after intercostal nerve blocks.[6] As these cases involved direct injection at thoracotomy, it has been postulated that intraneural injection was responsible, but inadvertent injection via a dural cuff has not been ruled out as a possibility. It is unlikely that direct intraneural injection occurred in the above patient as the catheter sited was under direct vision.

We postulate that the catheter was sited in an intervertebral foramen initially, and the tip migrated into the subarachnoid space. The catheter commonly in use on our unit at this time was that used for arterial monitoring. It had the advantage of a Luer connection, which is easily coupled with the continuous analgesia infusion systems available. To facilitate placement, it had become common practice to fashion a pointed tip on the catheter. This pointed tip could have penetrated the dura itself or cannulated a dural cuff.

Four changes have been made in our practice since this incident. Catheters designed for extradural siting are now used for paravertebral infusions. It is checked that the catheter tip lies in the paravertebral gutter before chest closure. This is usually visual though the use of a confirmation aid, such as a marked catheter tip, or observation of the overlying pleura on injection of saline, has been suggested. An aspiration test is performed before drug injection and, in addition, a 3 ml test dose of local anaesthetic is administered before the wound dressings are applied. Finally, the patient is monitored for evidence of subarachnoid injection before the therapeutic dose is given.

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BJA

COMMENTARY

Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia[†]

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Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disease triggered by several anaesthetic agents. The *in vitro* muscle contracture test (IVCT) is the standard test to establish an individual's risk of susceptibility to MH. Clinical practitioners and geneticists of the European MH Group have agreed on the present guidelines for the detection of MH susceptibility using molecular genetic techniques and/or IVCT to predict the risk of MH.

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Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disease triggered by commonly used potent inhalation anaesthetics and/or succinylcholine. The *in vitro* muscle contracture test (IVCT) is the standard test to establish an individual's risk of susceptibility to MH.[1] The European MH Group has developed a standardized protocol for the IVCT and has initiated and fostered international collaborative molecular genetic studies to investigate the molecular basis of MH. Data from these studies demonstrate that MH displays a high level of locus heterogeneity. Thus, it is not feasible to diagnose MH susceptibility, and, more specifically, to exclude MH risk, on the basis of a simple genetic test alone. However, it is of utmost importance to avoid false MH-negative (MHN) diagnoses because of the potential risk of MH during general anaesthesia for these patients and their offspring. These general obstacles notwithstanding, there may be specific situations where genetic data provide additional diagnostic information or contribute information independent of IVCT. It is the purpose of this document to outline recommended procedures for the potential diagnostic use of such genetic findings depending on the different clinical situations that may arise.

Referrals

The usual route of entry for individuals into MH investigations follows a suspected MH crisis and referral of the patient to an MH Investigation Unit, where diagnostic procedures and genetic counselling should be performed according to Figure 1.

IVCT

An IVCT is performed on the patient or, if the patient is too young or has not survived the anaesthetic event, his or her parents. If MH susceptibility status is confirmed by IVCT, then there is a clinical responsibility to offer the IVCT to the relatives of the index case, assuming autosomal dominant inheritance and starting with first-degree relatives.

Genetic investigations

Mutation analysis

At this stage, molecular genetic testing for causative mutations in the ryanodine receptor gene (*RYR1*) of the index case could lead to quicker results for the rest of the kinship. An up-to-date list of mutations that have been shown to directly alter RYRI caffeine or halothane sensitivity is shown in Table 1.

Genetic analysis should be performed in, or only after consultation with an MH Investigation Unit. Once a causative mutation has been detected in the proband or index patient, it can be used to test relatives who have not

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yet been tested by the IVCT. Mutation carriers should consequently be regarded as susceptible to MH. However, family members who do not carry the mutation observed in the pedigree should still undergo IVCT investigation. The reason for such caution is the observation in several pedigrees investigated by members of the European MH Group of discordance between genetic and IVCT results, implicating a second MH susceptibility gene segregating in the kinship.[23]

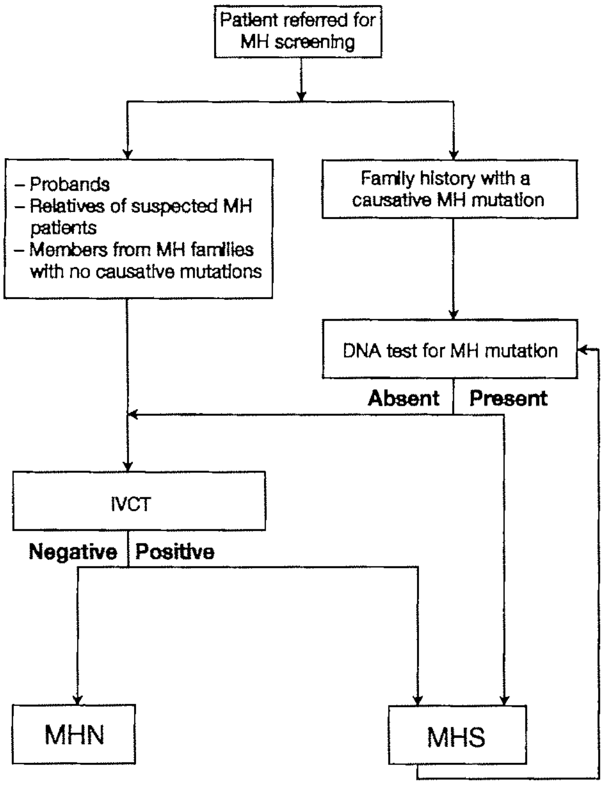
Patient referred for MH screening
- Probands
- Relatives of suspected MH patients
- Members from MH families with no causative mutations
Family history with a causative MH mutation
DNA test for MH mutation
Absent
Present
IVCT
Negative
Positive
MHN
MHS

Fig 1 Suggested route for MH susceptibility testing. IVCT=*in vitro* muscle contracture test; MHN=malignant hyperthermia negative; MHS=malignant hyperthermia susceptible.

Segregation analysis

Once the MH status of the extended pedigree (e.g. 10 informative meioses) has been determined by the IVCT, it may be possible to undertake genetic segregation analysis with markers close to known MH susceptibility loci. An up-to-date list of recommended markers and details of genetic modelling compiled by the European Malignant Hyperthermia Group, Genetics Section, is available on the internet (http://www.emhg.org).

Rarely, a single pedigree may be sufficiently large to establish linkage to a candidate locus with a high probability (lod score >3.0). In such a situation the question arises as to whether or not haplotype analysis can be used to assign MH status. Under these circumstances, individuals carrying the high-risk haplotype should be regarded as susceptible to MH even without confirmation by a positive IVCT. The converse is not true, that is, identification of the low-risk haplotype does not equate with MHN status and such individuals should have IVCT determination of their MH status.

In families where linkage to a candidate gene, *RYR1* or another locus, is suggested but not firmly established (i.e. lod score <3.0) haplotype analysis for predictive testing is not appropriate due to the high level of locus heterogeneity in MH. In such families, however, it is desirable to search for unknown mutations in the suggested candidate gene for research purposes.

Failure to reach a lod score of +3.0 in a single family due to the occurrence of a single individual in whom there is recombination between the haplotype and IVCT-deter-

Table 1 List of *RYR1* mutations potentially causative for MH susceptibility (MHS) and central core disease (CCD). Residue numbering within the *RYR1* nucleotide and amino acid sequence corresponds to the human *RYR1* sequence according to Zorzato and colleagues[18] (accession number J05200.1), updated according to Zhang and colleagues[16] and Phillips and colleagues.[19] Functional characterization of the *RYR1* mutations on RYR1 channel activity have been performed by calcium photometry on myotubes and/or COS-7 or HEK cells transfected with *RYR1* genes bearing the mutations[20–24]

Exon	Mutation position codon change	RYR1 amino acid change	Functional comparison with wild-type RYR1		Phenotype	Estimated incidence	Reference
			Caffeine sensitivity	Halothane sensitivity			
2	103TGC→CGC	Cys35→Arg	no difference	increased	MHS	one family	4
6	487CGC→TGC	Arg163→Cys	increased	increased	MHS and/or CCD	2%	5
9	742GGG→AGG	Gly248→Arg	increased	increased	MHS	one family	6
11	1021GGG→AGG	Gly341→Arg	increased	increased	MHS	6 – 10%	7
12	1209ATC→ATG	Ile403→Met	increased	increased	CCD; MHS unknown	one family	5
14	1565TAT→TCT	Tyr522→Ser	increased	increased	MHS and/or CCD	one family	8
15	1654CGG→TGG	Arg552→Trp	increased	increased	MHS	one family	9
17	1840CGC→TGC	Arg614→Cys	increased	increased	MHS	4 – 9%	10
17	1841CGC→CTC	Arg614→Leu	increased	increased	MHS	2%	11
39	6487CGC→TGC	Arg2163→Cys	increased	increased	MHS	4%	12
39	6488CGC→CAC	Arg2163→His	increased	increased	MHS and/or CCD	one family	12
45	7300GGA→AGA	Gly2434→Arg	increased	increased	MHS	4–10%	13–15
45	7304CGC→CAC	Arg2435→His	increased	increased	MHS and/or CCD	one family	16
46	7372CGC→TGC	Arg2458→Cys	increased	increased	MHS	4%	17
46	7373CGC→CAC	Arg2458→His	increased	increased	MHS	4%	17

mined MH status will require closer scrutiny and possible reassessment of the genetic and bioassay results to attempt to resolve the basis of the discordance. For predictive diagnosis in such families, the more conservative estimation, i.e. the higher risk outcome (either the MH susceptibility test result from the IVCT or the high-risk haplotype) should be the basis for the clinical decision.

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Phaeochromocytoma diagnosed during labour

Editor—We were interested to read the article by Strachan and colleagues[1] as we have recently managed a similar case of phaeochromocytoma undiagnosed antenatally, during labour and subsequently in the intensive care unit.[2] Despite the paucity of data about this rare endocrine emergency during pregnancy we would like to challenge certain aspects of the overall management.

The presumptive and fortuitous diagnosis of phaeochromocytoma during labour was made on the basis of a single hypertensive reading and glucose intolerance; the latter is not unusual in a patient diagnosed with gestational diabetes. We believe that hypertension in labour associated with headache is pre-eclampsia until proven otherwise and should be treated accordingly, i.e. epidural, magnesium, hydralazine. Alpha-blocking drugs do not routinely form part of the armamentarium of the management of pre-eclampsia. But magnesium has been found to be a useful adjunct in the management of both severe pre-eclampsia and phaeochromocytoma due to its calcium antagonist action. Calcium plays a fundamental role in stimulus response coupling of catecholamine release from the adrenal medulla and adrenergic nerve terminals.[3] Every labour suite in the UK should have ready access to magnesium and possess guidelines on how and when to administer the drug.

Harper and colleagues report[4] that an unrecognized phaeochromocytoma may be potentially fatal as hypertensive crises may be precipitated by vaginal delivery, the mechanical effects of the gravid uterus, uterine contractions and even vigorous fetal movements. Hence from the maternal standpoint, in the presence of a functioning epidural during a labour punctuated with high blood pressure readings, we are surprised that the decision to proceed with a vaginal delivery was taken; a view supported by Schenker and Grant[5] who believe labour and vaginal delivery should be avoided in such cases. Fetal hypoxia and death may also occur during these hypertensive crises. Phaeochromocytoma is the great mimic. In retrospect, the clues were present: headache, gestational diabetes, and hypertension.

The key to a better prognosis is early diagnosis and therefore despite our difference of opinion we congratulate the authors on their prompt consideration of such a rare diagnosis in pregnancy and the successful outcome.

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1 Strachan AN, Claydon P, Caunt JA. Phaeochromocytoma diagnosed during labour. *Br J Anaesth* 2000; **85**: 635–7
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Editor—Strachan and colleagues are to be congratulated on their diagnosis and management of a phaeochromocytoma during labour.[1] However, we were disappointed that magnesium was not mentioned as a possible treatment in the discussion.

Magnesium has a well established place in the management of both non-pregnant and pregnant patients with phaeochromocytoma,[2 3] where it has a marked anti-adrenergic effect and is effective in reducing catecholamine concentrations.[2] It has a number of different mechanisms of action, in particular inhibition of catecholamine release, as well as vasodilation and a reduction in the incidence of cardiac arrhythmias.[4] The anti-adrenergic effect is particularly desirable in a labouring patient as catecholamine surges may produce gross haemodynamic changes in the mother and severely compromise placental perfusion. Although a tocolytic, magnesium does not prolong or affect the duration of labour (although it may necessitate a higher dose of oxytocin).[5]

Whilst we accept that α and β blockade are important in the management of phaeochromocytoma in pregnancy (although the latter may cause fetal bradycardia), as well as the judicious use of an epidural, magnesium should be considered. The rarity of the condition will always prevent large studies, but magnesium is a safe drug with increasing usage. In particular, with its established place in the treatment of eclampsia, magnesium should be familiar to all obstetric anaesthetists, thus making it an ideal agent for the control of hypertension in these patients.[6]

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1 Strachan AN, Claydon P, Caunt JA. Phaeochromocytoma diagnosed during labour. *Br J Anaesth* 2000; **85**: 635–7
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Editor—Thank you for the opportunity to respond to the points raised by Bullough and Watters, and Fawcett and Edkins in our case report. We agree that hypertension during pregnancy (and labour) associated with headache is pre-eclampsia until proven otherwise. Pre-eclampsia is a syndrome of pregnancy including hypertension and proteinuria. Our patient never had measured hypertension or proteinuria antenatally. The sudden unexplained extreme rise and fall of blood pressure in our patient is not a recognized feature of pre-eclampsia appearing in labour. In retrospect, we were not surprised about her normal antenatal blood pressure readings. She had not had blood pressure measured during an attack before. In non-pregnant patients with phaeochromocytoma, 30% of patients have normal blood pressure between attacks.[1]

We agree that magnesium sulphate could be a possible alternative treatment option. It has an established role in obstetrics

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though its use in the treatment of pre-eclampsia is still under debate in the United Kingdom.[2] We opted to use the epidural and alpha blockade to control blood pressure. Alpha blockade has been used for the management of the vast majority of pregnant patients with phaeochromocytoma recorded in the medical literature with proven reduction in infant and maternal mortality.[3] Magnesium has been used as an alternative to alpha blockade in a small number of reported patients who had been stabilized with alpha blockade pre-operatively. Additional therapy was occasionally needed and magnesium failed to block the catecholamine release in all patients.[4] Magnesium has not been shown to be superior to alpha blockade as yet, but we agree that it should be considered as an option. We used alpha blockade because of the reasons outlined above and because of our familiarity with this regimen with non-pregnant patients with phaeochromocytoma.

The decision as to the mode of delivery was not easy as both vaginal delivery and Caesarean section had major risks. Resection of the tumour in an unprepared patient at Caesarean section would be dangerous. Thus Caesarean section seemed to have no obvious benefits over vaginal delivery, both allowing only the delivery of the baby. As we stated in our report the evidence from the literature after 1980 for one form of delivery over the other was inconclusive for this situation. We had the probability of a short second stage of delivery. After much debate with all concerned, including the patient's wish for a normal delivery, we committed ourselves to a trial of labour, but were prepared to change our plans if necessary. With so few patients diagnosed in active labour it will be difficult to scientifically answer this debate, but recent practice seems to have moved to allow some patients diagnosed as having a phaeochromocytoma to have a trial of labour. One institution elected to delivery vaginally four of eight patients diagnosed during pregnancy without loss of mother or baby.[5]

Finally, we would like to agree with Bullough and Watters that early diagnosis is the key to better prognosis and thus we must be watchful for the great mimic—phaeochromocytoma!

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Serum S100 protein as a marker of cerebral damage during cardiac surgery

Editor—We read with interest the review of serum S100 protein by Shaaban Ali and colleagues.[1] While we wholeheartedly agree with their premise, that identification of a serum marker to assist in the diagnosis of cerebral injury after cardiac surgery is potentially useful, we take issue with their choice of S100 itself. Accepting that elevations of serum S100 levels have been shown to be of some significance in diagnostic and prognostic decisions in several settings of cerebral injury (such as head injury and stroke), its value in cardiac surgery remains uncertain.

Despite numerous investigations (including our own), the distinct lack of a consistent relationship between S100 and cerebral outcome after cardiac surgery is puzzling. Although late elevation (occurring 24 h or more after surgery) may have a stronger relationship to cerebral outcome, the short term elevations (occurring within the first few hours after surgery) may entirely be due to extracranial contamination. If one accepts that S100 is present in mediastinal tissue and, therefore, in cardiotomy blood returned to the circulation,[2] then a link between S100 elevation and cerebral outcome begins to emerge. Cerebral outcome after cardiac surgery has been shown to be related to intra-operative cerebral microembolic load as quantified by transcranial Doppler (TCD).[3] We have previously shown that elevations in S100 after cardiac surgery are related to the number of TCD emboli.[4] Subsequent to this latter investigation, however, it has been shown that cardiotomy blood itself is a significant source of cerebral microemboli.[5] Therefore, if neurological outcome is related to cerebral microemboli, and use of the cardiotomy suction increases microembolic load, and the cardiotomy blood contains S100, then the relationship between S100 and cerebral outcome, although most likely erroneous, becomes entirely plausible.

We believe that having a reliable marker for cerebral injury will be of use, possibly for its early diagnosis, particularly when pharmacological neuroprotectants become available, but also in the investigation of neuroprotectants using the marker as an intermediate endpoint in phase II clinical trials. Reducing marker levels (whatever that marker may be) by a drug may be the 'proof of principle' that the drug developer needs in order to go forward with a larger, and more expensive definitive trial where a clinical outcome is sought. At present, however, we do not believe that there is any current value in S100 as a marker of cerebral injury following cardiac surgery.

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Editor—We welcome the opportunity to respond to the letter of Grocott and Arrowsmith. The points they raise with regard to extracranial sources of S100β protein are valid, but some consideration of the time-scale of S100β protein needs to be taken into account. The biological half-life of S100β protein is less than 1 h.[1] Therefore, to avoid extracerebral contamination of S100β samples, proper sampling times should be selected (~2 h after cardiotomy suction or autotransfusion).[2]

In our review, we explained that the early release of S100β after cardiopulmonary bypass (CPB) is associated with different pre- and peri-operative events and it is difficult to determine the exact cause of its release. In addition, the level of S100β protein at which stroke or any cerebral complication can be diagnosed is not entirely clear. Furthermore, the patterns of S100β protein give little or no information about the anatomical distribution of cerebral injury or its functional impact.[3] We agree that neurological and neurophysiological examinations should be considered as the gold standards in assessment of perfusion techniques and neuroprotective drugs. However, S100β protein warrants continuing consideration as an early indicator of cerebral injury, if extracerebral sources are eliminated. In particular, it can be measured at a time when other diagnostic techniques (e.g. neurological and neuropsychological examinations, CT scan, MRI) may not be suitable or are not able to detect such injuries.[3]

Secondary or late release pattern of S100β protein (15–48 h) in the post-operative period is a sign of further neurological injury,[4–6] unless there is ongoing autotransfusion from chest tubes.[2] Georgiadis and coworkers found that S100β protein levels at 24 h after CPB surgery have a sensitivity and specificity of approximately 90% and 97.4%, respectively, in identifying or excluding patients with or without cerebral injury.[6] Interestingly, Herrmann and colleagues showed that the most significant time window in which S100β may have a predictive value for diagnosis of neurophysiological and neuropsychiatric impairments is between 6 and 30 h after surgery.[7] Moreover, Abdul-Khaliq and colleagues found higher serum concentrations up to 22.5 μg litre^{-1} at 24 h after CPB in children who had seizures after cardiac surgery.[8] These studies[6–8] support the importance of the late release pattern of S100β protein in early detection of brain injury in children and adults after CPB.

We believe that with proper identification of extracerebral sources, and with better sampling times, S100β protein may be used to differentiate between the benefits and adverse effects of different perfusion strategies and neuroprotective drugs.

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The carina as a landmark in central venous catheter placement

Editor—The paper by Schuster and colleagues[1] is valuable in defining the anatomical relationship of the pericardium to the carina, and by inference to the carina as seen on x-ray. We agree that the ideal placement of a central venous catheter (CVC) tip is in the superior vena cava (SVC) above the pericardial reflection.

However, the statement that 'in all cases, the pericardial sac ends below the level of the carina' applies only to their sample and not necessarily to the underlying population. Their conclusions should be based on estimates of the variability between individuals. We would not be surprised if the carina was occasionally below the pericardial reflection in the wider population, but we would like to know how often we might expect it.

They report the carina to pericardial distance as a mean, SEM and range. If a normal distribution is assumed (with $n=34$ and SEM$=0.1$) then the standard deviation of their sample is about 0.6 cm. With this assumption we would expect 95% of the population to fall within the range of –0.7 cm to +1.5 cm; the negative sign indicating that the carina is below the pericardial reflection. It is likely, from the range given (0–2.1 cm) and from anatomical considerations, that the distribution is skewed to the right. If this were the case, the carina would be inferior to the pericardial reflection less often than we have assumed. It would be of interest to know whether their results can be transformed to approximate a normal distribution to allow prediction of the chances of the carina lying lower than the pericardial reflection.

Thus further information would be useful before we rely on this landmark for judging the tip position of CVCs.

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1 Schuster M, Nave H, Piepenbrock S, Pabst R, Panning B. The carina as a landmark in central venous catheter placement. *Br J Anaesth* 2000; **85**: 192–4

Editor—We agree with Crawford and colleagues that further investigations in a larger experimental group would be helpful for a more reliable definition of a landmark for central venous catheter placement. Thus, we are planning to investigate more corpses in this aspect. Furthermore, we are interested in any anatomical changes in the elderly compared with younger adults, or in adolescents and children.

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Safe placement of central venous catheters

Editor—I welcome the advice given by both groups of authors regarding the placement of central venous catheters.[1 2] The articles highlight concerns surrounding the risks of perforation of the cardiac chambers and great veins resulting from poorly positioned catheters and suggest various sites for correct catheter tip placement.

I feel both groups have failed to mention one simple and practical problem. Many central venous catheters are inserted by junior doctors who, particularly those from specialities outside of anaesthesia, find it necessary to insert the entire length of the catheter, irrespective of the route of insertion. As many hospitals only stock 20 cm catheters as standard, this will inevitably give rise to some of the complications outlined in the articles.

If hospitals were to make 15 cm catheters more widely available, this would overcome two particular problems. First, that of catheter tip position. By using shorter catheters, the likelihood of the tip lying in an unsatisfactory position must be less, although we must not detract from trying to achieve the ideal (whatever position that might be). Second, a shorter catheter alleviates the frustrating need to create ingenious loops of redundant catheter around the insertion site. I have not found the clip-on fixation devices to be particularly helpful, and it is not uncommon for patients or staff to hook a digit under the loop and inadvertently remove the catheter. In addition, it is well recognized that poor fixation allows excessive mobility at the insertion site—this increases the risk of perforation by the catheter tip and development of infection at the skin site.

I feel we need to alert hospitals and doctors to provide and use the correct tools for the job. Most manufacturers will supply 15 cm central venous catheters. The 20 cm catheters are unnecessary for the great majority of patients and yet we persist in using them.

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1 Fletcher SJ, Bodenham AR. Safe placement of central venous catheters: where should the tip of the catheter lie? *Br J Anaesth* 2000; **85**: 188–91
2 Schuster M, Nave H, Piepenbrock S, Pabst R, Panning R. The carina as a landmark in central venous catheter placement. *Br J Anaesth* 2000; **85**: 192–4

Editor—We would concur with Dr Cupitt's comments on the availability and use of 15 cm central venous catheters. It is important, however, that catheter selection is appropriate to the proposed route of insertion. For instance, the tip of a 15 cm catheter fully inserted via the left internal jugular approach might abut the wall of the superior vena cava (SVC) and be at high risk of perforation, whereas a similarly inserted 20 cm catheter would pass down the SVC such that the tip is coaxial with the vessel.

This raises the wider issue of training in central venous catheterization and the question of whether occasional practice is justifiable. Two logical conclusions might be for anaesthetists to play a greater role in hospital-wide training in vascular access or that anaesthetists should provide all central venous access. Clearly, both options would have huge implications for the workload of anaesthetic departments.

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Difficult intubation in a patient with benign masseteric muscle hypertrophy

Editor—I wish to report a case of benign masseteric hypertrophy in a patient who presented as a day case for routine dental surgery and who was predicted to be a difficult intubation requiring awake fibreoptic intubation. Benign masseteric hypertrophy is a rare condition, usually of unknown aetiology, in which there is unilateral or bilateral hypertrophy of the masseter muscle. This case illustrates that the condition may produce difficult conditions for tracheal intubation.

A 46-yr-old Caucasian, male patient was scheduled for an extraction of the lower right wisdom tooth under general anaesthesia. Anaesthetic assessment revealed a fit male with no significant past medical history, although his first words were 'Doctor, you are going to have problems with me!' His dentist had warned him that his airway was potentially difficult for the anaesthetist. He had benign masseteric hypertrophy with extremely limited mouth opening causing problems in eating; he had to cut food into very small pieces to fit into his mouth.

He was a non-smoker, on no medication and had no allergies. Physical examination was unremarkable, except for his airway. Routine pre-operative assessment showed limited mouth opening of 1–1.5 cm which was a grade IV in Mallampati's modified classification.[1 2] The surgical team thought local anaesthesia was not an option as access would be difficult, and it was assumed that some relaxation would occur under general anaesthesia. The patient was fully informed of the problems relating to his case and that the safest option was to proceed with an awake fibreoptic intubation. This technique was explained to him in detail. The patient was co-operative and agreed to the procedure. He was unpremedicated and in the anaesthetic room, standard monitoring was commenced (ECG, pulse oximetry, and non-invasive blood pressure). Intravenous access was obtained and glycopyrronium 0.2 mg was given as an antisialogogue. Sedation was given in increments to a total of midazolam 2 mg and fentanyl 20 µg intravenously. Topical anaesthesia of the nasal passages was achieved using a combination of 1.0 ml of topical 4% lidocaine (diluted to 2% with 0.9% saline), injected into each nostril. Into the left nostril three cotton buds impregnated in 5% cocaine was also inserted for 10 min. For the oral cavity, 5 ml of 2% lidocaine gel were given and the patient was asked to move it around in his mouth for two min and then to swallow it. The procedure was then repeated. A cricothyroid puncture was performed using a 22 G cannula inserted through the cricothyroid membrane. Injection of 1.5 ml of a mixture containing 3 ml of topical 4% lidocaine (diluted up to 5 ml with 0.9% saline) was performed at the end of a deep inspiration, and repeated once. After checking for adequate anaesthesia, a 6.5 mm internal diameter reinforced tracheal tube was inserted under fibreoscopic guidance through the left nostril without problems. On confirmation of tracheal placement using the capnograph, anaesthesia was induced with an intravenous bolus of propofol 2.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} was given and anaesthesia was maintained with oxygen in air and isoflurane 1–2%. Direct laryngoscopy was performed at this point. The mouth opening had not improved; laryngoscopy was very difficult being a grade 3 in Cormack and Lehane's classification[3] with a downward pointing epiglottis.

For analgesia, fentanyl 100 µg, and morphine 5 mg were given with diclofenac 100 mg administered rectally. Consent had been obtained pre-operatively for the suppository. Surgical access to the tooth proved extremely difficult but enough mouth opening was achieved for the tooth to be removed. Local infiltration with 5 ml of 0.5% bupivacaine was done by the surgeon to help with post-operative pain relief. Residual muscle relaxation was reversed after 50 min with neostigmine 2.5 mg and glycopyrronium 0.5 mg and the patient was fully awake within 10 min, still with the tracheal tube in place. He was extubated and sent to recovery without any further problems. Post-operatively, he was advised to join the Medic-Alert scheme, and always to warn anaesthetists of this problem. Three weeks later, the patient was reviewed in the surgical clinic with no problems except for limited mouth opening that was unchanged.

Masseteric muscle hypertrophy is a clinical condition in which there is an increase in the size of the cells and an overall enlargement of the muscle itself. The condition usually occurs in late adolescence and is more common in males than females.[4] The aetiology of the condition is unexplained. The acquired enlargement represents work hypertrophy, most frequently following clenching, bruxing during sleep, and constant gum chewing. It is often associated with dental wearing. A congenital variety also exists, but it is far less common.[4 5 7]

The main complaint is of an unwanted cosmetic appearance due to facial asymmetry (unilateral) or too broad a face (bilateral), the so-called 'masseteric look'.[4 5] Some individuals also complain of pain, usually of a mild nature, or some limitation of mouth opening.[5] The diagnosis of this condition is based on awareness of the existence of this pathology, the clinical and radiographic findings, and exclusion of more serious pathology.[6] Our patient had the typical 'masseteric look' (Fig. 1) of this condition, but the clinical complaints were atypical. He did not have any cosmetic complaint nor any pain or discomfort. The main problem was of severe limitation of mouth opening which made simple tasks such as eating very laborious (Fig. 1b). The mild discomfort was associated with repeated inflammation of his infected wisdom tooth.

The main issue for anaesthesia was the severe limitation of mouth opening. A literature search did not reveal any previously reported cases of severely limited mouth opening with difficult intubation in patients with masseteric muscle hypertrophy. We thought that the limitation of mouth opening may be due to a degree of trismus caused by inflammation of the repeatedly infected tooth. However, general anaesthesia and muscle relaxation failed to produce any improvement. Post-operatively, the patient had the same limitation of mouth opening and was still a grade IV on the modified Mallampati's classification. The severe limitation of mouth opening was an intrinsic characteristic of his masseteric muscle hypertrophy syndrome.

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Internal jugular venous cannulation complicated by J-tip guide wire entrapment

Editor—We report an unusual complication of internal jugular venous cannulation with a J-tip guide wire.

A 62-yr-old female patient was admitted to the coronary care unit after an episode of central chest pain and dizziness. Acute myocardial infarction was diagnosed. She had a past medical history of rheumatoid arthritis, osteoporosis and kyphoscoliosis of the thoracic spine with chronic obstructive pulmonary disease. She was hypotensive on admission with a blood pressure of 85/51 mm Hg, and oliguric. Central venous

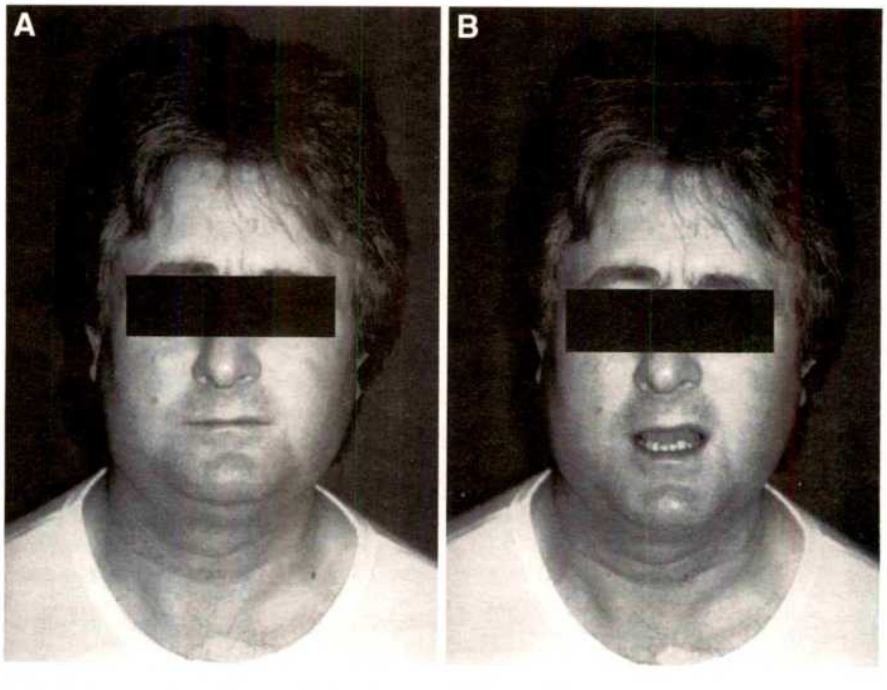

Fig 1 The patient's limited mouth opening (B) compared with the closed state (A), is apparent.

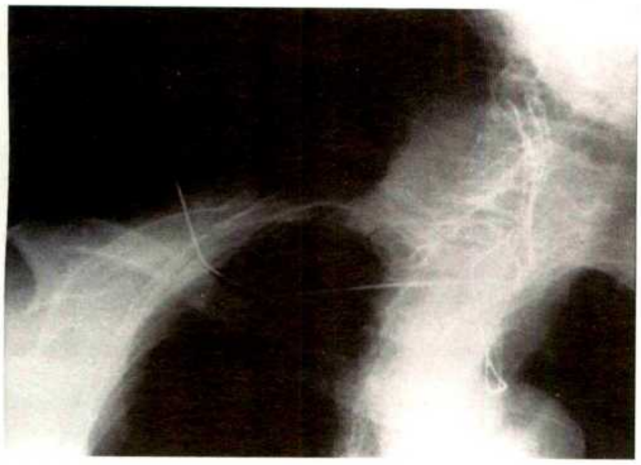

Fig 1 Close up view of entrapped guide wire.

cannulation of the right internal jugular vein was planned by an experienced physician. A pre-packaged Seldinger-type triple lumen kit (Hydrocath-Becton Dickinson critical care system plc Ltd) was used. It consisted of a catheter 7Fr/2.4 × 200 mm (16G:18G:18G), a J-tip guide wire 0.9 × 700 mm, introducers 1.4 × 70 mm, and 1.7 × 70 mm, and a dilator (8Fr). The procedure was explained to the patient by the doctor. Under aseptic conditions and after confirming the landmarks, the physician inserted the introducer needle and achieved good venous return. The guide wire was inserted with minimal resistance up to 25 cm. The triple lumen catheter was then inserted, but the guide wire could not be removed despite several attempts with gentle traction. A portable chest x-ray was obtained and revealed looping of the guide wire (Fig. 1). A consultant surgeon was called and the patient was taken to the operating theatre for surgical removal of the looped guide wire.

Exploration showed that the guide wire had passed through the anterior wall of the internal jugular vein into the extravascular space, and coiled up in the sternocleidomastoid muscle and subcutaneous tissue. The guide wire was removed uneventfully.

The placement of central venous catheters is a technically challenging procedure with known risks and complications. The majority of the complications are preventable if adequate precautions are taken. Complications may involve inserting the needle, the guide wire, the dilator, or the catheter. The performing physician's skill also plays an important role. Although catheter looping and knotting are well recognized as complications of central venous catheterization, there are few reports of guide wire looping, knotting or entrapment.[1 2] In the case report by Wang and Sweeney, a straight and relatively stiff solid core guide wire *without* a J-tip may have been an aggravating factor in causing guide wire looping and entrapment.[2] But Kjeldsen reported a case of transvenous misplacement and loop formation of a relatively flexible spring guide wire. The author suggested that occlusion due to thrombosis in the vessel wall might explain the ease with which the soft end of the wire had pierced the vessel.[3]

In this report, we hypothesize that the guide wire, after entering the internal jugular vein, might have pierced the wall of the vein and gained access to the extravascular space. Altered landmarks due to kyphoscoliosis might have contributed to the complication described. Wang and Sweeney suggested that 'if a J-tip guide wire is not used, particular attention should be given to the risk of the guide wire lodging against or perforating the vessel wall'.[2] The introduction of an excessive length of guide wire during placement of central venous catheters through the internal jugular vein can result in rare but significant complications. In most cases, 18 cm should be considered the upper limit of safe guide wire length to be introduced in adults.[4]

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1 Wang LP, Einarsson E. A complication of subclavian vein catheterisation. Extravascular knotting of a guidewire. *Acta Anaesthesiol Scand* 1987; **31**: 187–8

2 Wang HE, Sweeney TA. Subclavian central venous catheterization complicated by guidewire looping and entrapment. *J Emerg Med* 1999; **17**: 721–4

3 Kjeldsen L. Transvenous misplacement and loop formation of spring guide wire. *Anaesthesia* 1987; **42**: 216–7

4 Andrews RT, Bova DA, Venbrux AC. How much guide wire is too much? Direct measurement of the distance from subclavian and internal jugular vein access sites to the superior vena cava–atrial junction during central venous catheter placement. *Crit Care Med* 2000; **28**: 138–42

A handmade device for difficult intubation

Editor—We read with interest the case report by Tashayod[1] describing two cases of difficult intubation managed by a handmade cuffed pharyngeal tube (CPT).

We attempted to construct the device using the components and technique described and found it not only difficult to make but also, and more importantly, unreliable in cuff inflation. We fully appreciate the issues of cost and availability of the equipment designed to manage the difficult airway and/or intubation but wonder if we would feel comfortable relying on the CPT in such circumstances.

Having ascertained the potential design faults, we would like to raise the issue of its use in the two cases of difficult airway/intubation. Whilst again acknowledging differing techniques, in the discussion it is stated that 'when a difficult airway is suspected spontaneous respiration should be maintained', and yet this principle is not followed in either case.

The technique of intravenous induction with muscle relaxation in these particular patients is potentially dangerous and despite the success in maintaining an airway perhaps some fundamentally safer techniques should have been mentioned, albeit briefly, in a journal read by trainers and trainees alike.

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1 Tashayod ME. Two cases of difficult intubation managed by a handmade device. *Br J Anaesth* 2000; **85**: 626–8

Editor—Tashayod[1] describes a novel 'hand-made' airway aid (the cuffed pharyngeal tube, CPT) which it is claimed is readily constructed with available materials (a tracheal tube and surgical glove) and of use for the patient with a difficult airway and/or intubation. It may indeed be the case that this device has a role in airway management, although probably very similar to the laryngeal mask airway (LMA[†]), and will certainly require extensive validation. Of more immediate concern are the techniques of airway management outlined in the two case reports—I believe the management strategies were wrong and, especially in the first patient, were probably dangerous.

Case 1 was a large, muscular athlete of 116 kg. He had a 'bushy beard' and was graded a Mallampati 4 prior to anaesthesia. He also had a known history of difficult intubation. After induction of anaesthesia and administration of a muscle relaxant, the patient was found not only difficult to mask ventilate but had an 'immobile' jaw and 'head extension was impossible'. Laryngoscopy was a grade 3 to 4 and as part of the planned procedure (for which the author had consent) the CPT was used as the airway of choice. This patient showed multiple warning signs of a difficult intubation from his general build to more formal assessment and inability to perform laryngoscopy must have been almost certain.[2] Furthermore, there would be a strong suggestion of difficult mask ventilation and therefore a technique of inducing anaesthesia and administering a muscle relaxant risks both being unable to intubate and losing the airway. To rely on an experimental device with no robust field testing in elective cases (let alone a difficult airway) must be questioned and having lost the patient's airway in this manner what was the next option? 'Plan A doesn't kill people, it is the lack of plan B'. In case 1, plan A was highly questionable and I cannot see where plan B would come from.

Case 2 must also be examined critically (as the author does during the discussion) where a patient in cervical 'halo' traction for surgical cervical fusion was induced and given succinylcholine 100 mg. Laryngoscopy 'was difficult' and a further dose of muscle relaxant (pancuronium 6 mg) was given to facilitate further attempts at laryngoscopy (unsuccessfully) and then the CPT was used successfully.

Again a difficult airway must have been expected in this patient[3] but I fail to see the rationale behind the use of a long-acting relaxant when an optimal dose of succinylcholine failed to provide the required conditions. Pancuronium, in any dose, would not have improved the view, increased the risk of losing the airway irreversibly, and must have encouraged repeated laryngoscopy risking airway trauma and hypoxaemia.

I would hold that there was one optimal management of both these difficult airways—and it is neither a new nor original technique. Both these patients should have had awake fibreoptic intubations, with no relaxant given until the airway is secure. It is hard to argue otherwise (with the possible exception of a spontaneously breathing gas induction)—and one should have strongly considered a regional technique for Case 1, who was to have hand surgery. The use of a non-validated 'home made' airway in cases of anticipated difficulty cannot be justified and raises serious questions over how informed the Case 1 'consent' must have been. Guidelines over airway management are readily available[4 5] and have widespread support—it is disappointing to see clinicians exploring dubious and probably dangerous techniques for no clear reason or benefit.

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1 Tashayod ME. Two cases of difficult intubation managed by a handmade device. *Br J Anaesth* 2000; **85**: 626–8
2 Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *Br J Anaesth* 1992; **68**: 90–7
3 Crosby ET, Lui A. The adult cervical spine: implications for airway management. *Can J Anaesth* 1990; **37**: 77–93
4 American Society of Anesthesiologists. Practice Guidelines for Management of the Difficult Airway. *Anesthesiology* 1993; **78**: 597–602
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Editor—I appreciate the concerns of Carroll and Williams, and Morris regarding my recent case report. I was delighted to learn that the principle of the CPT has not been criticized. I agree with the authors that the construction of the CPT with its asymmetric cuff is sophisticated. When the project started I had much difficulty in obtaining the desired configuration. But it was worthwhile in order to make a cost-free, hand-free, and efficient adjunct to manage 'The expected cases of difficult intubation'.

Surprisingly, the CPT has proved to be effective even when its configuration is not ideal; its pharyngeal ring is useful in management of the difficult airway. I hope that the CPT will be produced commercially in the near future.

In regard to our anaesthetic technique, we do not have the privilege of working with the newer intravenous and inhalational drugs available in some countries. However, in our first case I do not think that repeated administration of intravenous agents with close control of the state of consciousness and two injections of gallamine 40 mg would stop spontaneous respiration in a 116 kg muscular man. The use of a large dose of relaxant in the second case was, in retrospect, inappropriate. This case was included as it represents a case of 'unexpected difficult intubation' where the ease of insertion, efficiency and ready availability of the CPT promises a new option.

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[†] LMA® is the property of Intavent Limited.

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Book Reviews

The Brain and Cardiac Surgery. Causes of Neurological Complications and their Prevention. Stanton P. Newman and Michael J.G. Harrison with David A. Stump, Peter Smith and Ken Taylor (editors). Published by Harwood Academic Publishers. Pp. 343; indexed; illustrated. Price £70. ISBN 90-5702-476-4.

This is a timely book which discusses all forms of neurological damage following cardiac surgery. It is a multi-author volume with over 40 contributors from the UK and USA, the majority of whom are well-known experts in their fields. The principal editors are internationally renowned for their investigation into cerebral complications following cardiac surgery.

The text covers, in 17 chapters, the main topics of: the nature of the problem, monitoring and mechanisms of cerebral injury, surgical and anaesthetic practice, and special problems. This final section contains chapters discussing cerebral damage relating to heart transplantation and paediatric cardiac surgery. The latter chapter by Richard Jonas of Boston Children's Hospital describes succinctly seminal work carried out at that institution which has helped define the causes of neurological injury during cardiopulmonary bypass in children, thereby improving their intra-operative management.

Each chapter in the book is designed to be read independently. As a result there is considerable overlap of material between some chapters. This can be regarded as a benefit to the reader in a reference book of this calibre, because more than one viewpoint is expressed on difficult or controversial topics.

It is difficult to pick out highlights from this book as the chapters are of a uniformly high standard and profusely referenced. The introductory chapters by the main editors Stanton Newman and Michael Harrison, however, are very well constructed and easy to read. I particularly enjoyed the section on peripheral nerve damage in chapter 2 as this is a subject largely neglected in the context of neurological damage following cardiac surgery. The chapter on neuropsychological outcome puts a difficult subject into perspective and explains the evaluation and the methodological issues surrounding these assessments in a straightforward and understandable manner. Topical subjects covered extensively in the book include embolic damage, acid-base management in adults and children, over-heating of the brain and the pre-operative risk assessment of patients.

In general I have few criticisms of the book. It does not contain a great deal of material covering 'off-pump' cardiac surgery and the hazards of blood and platelet transfusion in the context of cerebral damage. This is perhaps not surprising, in view of the gestation period of a book of this nature, as 'off-pump' cardiac surgery is still in its infancy and there is little detailed information regarding its effects on the brain.

This book will be of interest to all those involved with patients undergoing cardiopulmonary bypass, particularly as cerebral injury remains a major cause of death and disability following cardiac surgery. It should be available in the library of all cardiac units and accessible to both cardiac surgeons and anaesthetists in training. At the listed price, this well-produced book is good value for an individual consultant cardiac surgeon and anaesthetist to buy for their personal use. It will save the endless hours searching the past literature and provide a sound basis for an understanding of future publications on the subject of brain injury in cardiac surgery.

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Regional Analgesia in Obstetrics: A Millennium Update. Felicity Reynolds (editor). Published by Springer-Verlag, London. Pp. 395; indexed; illustrated. Price £50. ISBN 1852332808.

Soon after the formation of the Obstetric Anaesthetists Association 30 years ago, Andrew Dougherty hosted a meeting at Kingston-upon-Thames where a group of obstetric anaesthetists met to extol the virtues of epidural analgesia for labour pain. The late Professor Utting reported the proceedings in the following terms: 'it would have been a brave man who had mistakenly got up and shouted that epidural analgesia was bunk; one could only pray that his end would be mercifully swift'. Since then regional anaesthesia in obstetrics has come of age and in this book, the fourth in a series of 10 yearly reviews, Professor Reynolds has called upon an impressive group of luminaries to produce a most scholarly and scientific text.

In the first section of the book contributors from many parts of the world provide a fascinating and rather disturbing insight into the varied obstetric and anaesthetist practices prevailing in their respective countries with the ability to pay, in many cases, seemingly the most important determinant of the quality and type of care. The large remainder of the book has a very strong British flavour in which new techniques, drugs, indications, and complications together with research methods, medical legal aspects, and issues of consent are fully discussed. With few exceptions the chapters are models of clarity, brevity and authority; none more so than those contributed by the editor herself. Most are strongly evidence-based with abundant relevant and up-to-date references but where such evidence is lacking very sensible and clinically sound recommendations are offered. The quality of editing is very high. Tables which are always adjacent to the relevant text are widely used making complex data easily understood. There is surprisingly little repetition, and I was proud to discover one printing mistake.

This book is a testament to the high standard of obstetric anaesthesia in the UK with its maternal mortality at an almost irreducible low. The vast majority of procedures are now performed under regional anaesthesia for which there appears to be very few contraindications; fears of long-term backache and neurological damage have proven unfounded.

We are reminded, however, that accidental dural puncture remains a serious problem, that epidural analgesia for labour still requires expert and attentive midwifery management, and that Tuffiers line must be respected when using atraumatic spinal needles, if conus damage is to be avoided.

The quality of contributions to this fine book is a fitting tribute to the editor's own enormous scientific and practical contribution to the specialty. No self-respecting obstetric anaesthetist should be without it.

R.G. Wilkes
Liverpool

Problems in Anesthesia, volume 12 number 2, April 2000. J.M. Neal, M.F. Mulroy and S.S. Liu (editors). Published by Lippincott, Williams and Wilkins, London. Pp. 232; indexed; illustrated. Price US$63. ISSN 0889-4698.

Problems in Anesthesia is a quarterly American publication under the editorship of Drs Fleisher and Prough. It has ten chapters written by a total of 19 authors on various aspects of regional anaesthesia. It aims to centre around controversies, difficulties and state of the art developments of the craft. Being a slim book, it

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carries easily and every word of it can be read in not many sittings.

The first three chapters are about upper limb, lower limb, and neuraxial blockade respectively and each gives a discourse on standard techniques and their problems. There is repetition of various topics and even then, authority is lacking in the answers to some questions. An example is the use of vasoconstrictors in local anaesthetic solutions. Perhaps this might have been better dealt with as a specific chapter or section on its own with a comprehensive literature review—the reader is left with no clear message about the question of benefit or risk using vasoconstrictor additives.

This reviewer was puzzled by the title choice of chapters four and five: 'Regional Anesthesia for Ambulatory Surgery' and 'Office Based Regional Anesthesia'. There is no clear definition or differentiation of these in the text and a considerable overlap occurs. Surely they would have been better united as one chapter.

Specialized practice within regional anaesthesia is covered in separate chapters on 'Acute Pain Management' and 'Obstetric Anesthesia'. The former concentrates on neuraxial opioids with and without the addition of a long-acting local anaesthetic. It touches on multimodal techniques for pain control and accelerated recovery regimens designed to minimize GI paresis and promote early voluntary musculoskeletal activity. The obstetric chapter confines itself to the possible link between neuraxial blockade and maternal fever and neonatal sepsis. Also discussed in this chapter are combined spinal epidural techniques and, as a separate section, how to deal with the morbidly obese parturient. Obesity is a more frequent phenomenon in North American medicine than elsewhere.

The last three chapters delve into 'Outcome and Effectiveness', 'Neurologic Complications' and 'Toxicity of Agents'. In Neurologic Complications there is a section on the hazards of low molecular weight heparin. It would have been helpful to specify and reference the 'European experience on the treatment (with LMWH) of patients undergoing spinal and epidural blocks'. There is minimal reference throughout the book to the literature outwith North America nor many references later than 1997.

Discussion on sterility and asepsis in the performance of neuraxial blocks would have benefited from reference to worldwide publications on these issues—in particular the wearing of face masks. There is no discussion on skin preparation. The controversy of regional anaesthetic techniques performed on anaesthetized or heavily sedated patients is debated in the context of North American rather than world literature. The reader is left without a clear message on the fundamental issue of risk *versus* benefit in the practice of regional anaesthesia which is disappointing in a text compiled by invited experts.

A previous review in the series concluded 'this is not a textbook for the trainee, neither is it a comprehensive reference book for the practising anaesthetist'. The same is true here though in fairness, for some of the problems, there are as yet no satisfactory answers and the editors have at least attempted to communicate the questions. The preface states that the monograph 'aims to provide a state of the art view of regional anesthesia and analgesia'. Though I think this has been partly achieved in an elegant production, there are some points of view which would stimulate debate outwith North America. It is an interesting read for anyone who practises regional anaesthesia.

I. Levack
Dundee

Sex, Gender and Pain. R.B. Fillingim (editor). Published by IASP Press, Seattle. Pp. 393; indexed. ISBN 0-931092-35-3.

This excellent book is another in the series from the International Association for the Study of Pain (IASP) Press on Progress in Research and Pain Management. It fulfils the mission statement of the organization in that it provides a timely, high quality, low cost publication about a current pain problem. During the 1990s, there has been increased interest in the influence of sex and gender on pain. There have been National Institute of Health initiatives and conferences about this important topic. There is now an IASP special interest group on sex, gender and pain.

Roger Fillingim who is a recognized expert in the field edits this book. The text brings together basic scientists and clinicians who explore the mechanisms and clinical importance of sex and gender differences in pain. There is something in this book to interest everyone. The text asks as many questions as it answers and gives many ideas for future research. The multi-factorial nature of the influence of sex and gender on pain is a recurrent theme, which involves the interaction of biological and psychological factors. This book is divided into four parts. Section I covers basic considerations for sex, gender and pain research. It has four chapters with a good mix of laboratory-based and biopsychosocial topics. Section II, on sex-related differences in experimental pain responses, has seven very good chapters covering diverse areas. The chapters on visceral pain by Maria Giamberardino, and sex-related analgesic responses by Christine Miaskowski and colleagues were particularly good. Section III covers sex-related factors in clinical pain conditions. It has six chapters covering epidemiology, headache, fibromyalgia, TMJ pain, IBS, and female genital pain. The final section IV was a single chapter by Karen Berkley on male *versus* female pain. This provided an excellent summary of current knowledge and ideas for the future. This book is a must have for all departments and individuals involved in the study and management of pain. It supports the notion that men may be from Mars and women may be from Venus after all!

K.H. Simpson
Leeds

Hypertext Book of Pulmonary Artery Catheterization, on CD-ROM. D.A. Pybus. Published by D.A. Pybus, Kogarah, Australia. Price Aus$50.

Dr Pybus and two colleagues, cardiac anaesthetists from Sydney, Australia, have created an excellent resource for anyone involved with pulmonary artery (PA) catheters. Much of the information is relevant to central venous catheters as well. In some ways the title of the CD-ROM is misleading, because not only is the text comprehensive and extremely well referenced, but they also include both a simulator that allows users to experience the problems and pitfalls of insert PA catheters and an interactive model of cardiorespiratory physiology. Although aimed primarily at those new to the subject, there is much for even the advanced practitioner.

The CD-ROM is compatible with Windows 98, Windows NT 4.0 and Windows 2000. The author states that it may run on Windows 95, but we have experienced problems when trying to do so. The hypertext format allows users to navigate easily through the 40 text chapters, as with a conventional book, but in addition provides links to over 100 illustrations, four computer videos and over 300 references. Placing the pointer over a reference number causes the reference to 'pop up', whilst clicking on a figure reference opens the picture in a new window. Specific keywords are highlighted; clicking on these takes the reader to a relevant chapter or page of further discussion. Navigation through the book is by 'point and click' and by means of forward, back and 'retrace' buttons. 15 MB of hard drive space is required, with the videos running direct from the CD drive. At present the book runs in a specific hypertext window; however the author is planning a web-browser based version, which should be more familiar to the internet literate.

The hypertext book covers all aspects of PA catheter usage, with detailed descriptions of insertion techniques using pictures from the 'sectioned human' projects and video clips. The depth of the work is evidenced by the inclusion of such details as a description of the pressure waveform should the catheter enter the coronary sinus. There is also a page listing the cognitive skills that are deemed necessary for the use of PA catheters, which will be of use to those designing teaching programmes.

The authors explore the controversy surrounding the use of PA catheters and include a section on evidence-based practice. The discussion is comprehensive and well referenced though the authors' (understandable) bias in favour of PA catheters is obvious, particularly when they address the 'pros' and 'cons' of the PA catheter compared with other forms of haemodynamic monitoring. The chapter on complications is wide-ranging and up-to-date.

The authors go beyond the insertion techniques and complications, exploring cardiorespiratory physiology and pharmacology. This is where the computer simulation comes into its own. The user manipulates a virtual PA catheter by means of buttons controlling balloon inflation and catheter advancement. 'Real time' ECG and pressure waveforms react appropriately. Although the graphics are not state of the art, they are realistic enough to give one that sinking feeling when an arrhythmia occurs. At this point, the defibrillate button becomes useful! The model is intelligent and prompts users when errors are being made; for example, withdrawing the catheter with the balloon inflated. To complement the physiological information, another window reveals the path of the PA catheter superimposed on a chest radiograph. The model can simulate not just the normal patient but also pathological states such as pulmonary hypertension and acute myocardial infarction. The user can adjust the propensity to arrhythmias during insertion.

The cardiorespiratory model permits an exploration of oxygen delivery and consumption, for example the degree of shunt can be altered and the effect on arterial oxygenation seen. In addition, there is an interactive model of the haemoglobin dissociation curve which permits the effect of changes in pH and Pa_{CO_2}, for example, to be studied.

Overall, we have no hesitation in recommending this CD-ROM to individuals and institutions. Learning resources such as this probably represent the future of medical education and one can foresee a time when their use would be required before trainees are allowed to carry out procedures in real life. What might be useful would be the purchase of 'institutional licenses' where a larger fee would permit copies to be made and allow widespread usage within a department, single copies are likely to be 'borrowed' and never seen again! Up-to-date information on this product can be found at www.manbit.com

S.J. Fletcher
A.R. Bodenham
Leeds

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British Journal of Anaesthesia **86** (**2**): 301–2 (2001)

Errata

*Production of human albumin solution: a continually developing colloid (BJA 2000; **85**: 887–95)*

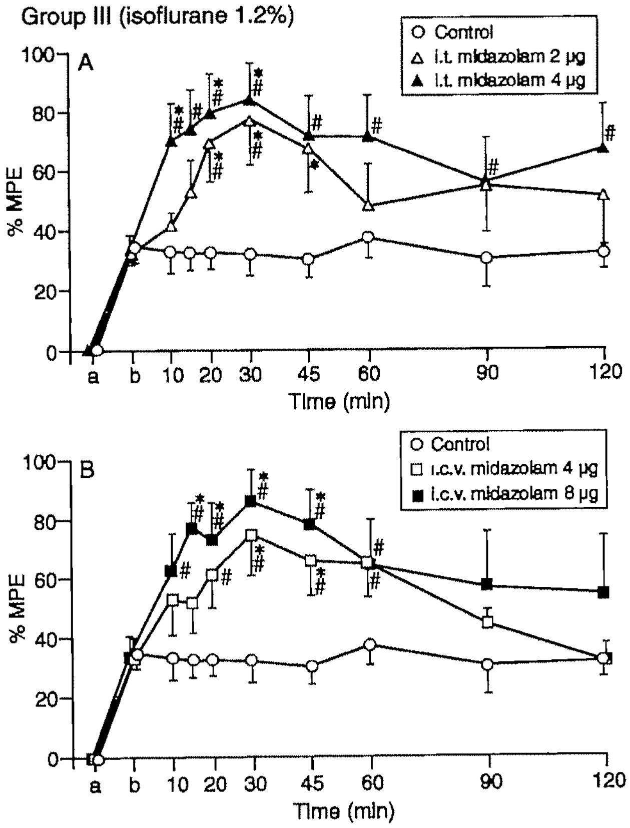
The units for aluminium in column 1 of table 1 on page 889 were published incorrectly. They should read as follows:

$\mu g\ \text{litre}^{-1}$

The publisher apologizes for this error.

*Spinal and and supraspinal midazolam potentiates antinociceptive effects of isoflurane (BJA 2000; **85**: 881–886)*

Figure 1 on page 883 was labelled incorrectly. The correct labelling is as follows:



The publisher apologizes for this error.

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Blood alcohol concentration and psychomotor effects (BJA 2000; 85: 401–6)

The dose of alcohol (page 402, Methods, paragraph 2, line 15) should read as 0.75 mg kg^{-1} (not 0.75 g kg^{-1} as quoted in the text) and, in the legend to Figure 1 on page 403, the oral dose should also read as 0.75 mg kg^{-1} (not p. 75 0.75 ml kg^{-1} as quoted in the text).

The author apologizes for not noticing these errors sooner and would like to thank Professor Mapleson for pointing them out.

Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers (BJA 1997; 79: 433–439)

The target concentrations on page 434, first column, line 14 should read as 0.5–2 µg ml $^{-1}$ (not mg ml $^{-1}$ as quoted in the text).

The publisher would like to thank John Sear for pointing out this error.

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BJA

ABSTRACTS

Proceedings of the Anaesthetic Research Society

Hammersmith Hospital, Imperial College School of Medicine

November 16–17, 2000

*The name of the author presenting the paper is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of relevant Human Ethics Committee or Animal Experimental Review Committee.*

VERBAL PRESENTATIONS

Nimodipine and acute postoperative pain

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There is growing experimental evidence that nimodipine enhances the antinociceptive properties of morphine.[1] Clinical studies of nimodipine on opioid use in cancer patients have shown either an opioid-sparing effect[2 3] or no effect[4] on analgesic requirements. In a volunteer study, nimodipine failed to demonstrate an analgesic effect when given with morphine.[5] We tested the hypothesis that oral nimodipine taken 6 hourly for 48 h postoperatively would reduce pain scores and morphine consumption in patients with acute postoperative pain.

Fifty-two patients undergoing total knee replacement surgery (age 70 (7) yr, 28 male) were allocated randomly to receive capsules containing either nimodipine 30 mg or placebo, in a double-blind study design. All patients received three capsules (nimodipine 90 mg or placebo) 1–2 h before induction of anaesthesia. Spinal anaesthesia was induced with hyperbaric bupivacaine 0.5% (2.4–3.0 ml) and fluids and ephedrine were given at the discretion of the anaesthetist. Morphine patient controlled analgesia (PCA, bolus 1 mg, lockout 5 min) was given for postoperative analgesia. Primary outcome measures were visual analogue pain scores (VAS) at rest and on moving (sitting forward) and PCA morphine consumption. The data were inspected for distribution using the Kolmogorov-Smirnov test. VAS pain, area under the pain relief curves and morphine consumption were compared using ANOVA with post-hoc Dunnet's test or unpaired *t*-test as appropriate.

The groups were similar in terms of age and gender distribution. Twelve patients were excluded from the analysis for various reasons. PCA morphine consumption is shown in Table 1. There were no significant differences in VAS pain, scores at rest or moving or in total pain relief. Lowest recorded systolic arterial pressure was also similar in the two study groups.

Table 1 PCA morphine consumption (mean (SD))

Time postoperative (h)	Nimodipine (n=20)	Placebo (n=20)	ANOVA and Dunnet's post test
2	7.0 (5)	5.1 (5.0)	P=0.27
4	17 (7)	15.0 (8.1)	P=0.42
6	26.4 (8)	21.6 (11)	P=0.13
8	31.5 (11)	25.3 (13)	P=0.11
12	38.7 (15)	29.4 (15)	P=0.047
24	62.1 (23)	45.1 (23)	P=0.031
48	87.9 (34)	61.3 (33)	P=0.026

Our study has demonstrated increased morphine consumption after 12 h in postoperative patients receiving nimodipine, suggesting that, in this situation, it inhibits the analgesic effect of morphine. This conflicts with previous clinical studies.

Keywords: pharmacology, nimodipine; pain, acute; calcium channel block, nimodipine

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Long-term management of pain of non-malignant origin with implanted intrathecal drug pumps

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There is limited literature of the role for long-term spinal drug administration systems in patients with chronic non-malignant pain. To our knowledge there is only one published study of reasonable sample size and duration that has addressed this with delivery limited to morphine sulphate.[1] In the UK the commonest drug delivered is diamorphine, often with bupivacaine and/or clonidine and/or baclofen. It remains controversial whether this unimodal therapy improves pain and quality of life in the long-term in those with non-malignant pain. The objective of this study was to evaluate the long-term outcome of this therapy on the biopsychosocial dimensions of chronic non-malignant pain.

A retrospective patient questionnaire study of the efficacy of this therapy utilizing third party analyser was conducted. Pain and a range of quality of life measures were recorded on an 11-point numerical rating scale.[2] Patients recorded present scores and those recalled before spinal implant. Our null hypothesis was that this unimodal therapy would have no benefits long term on pain of non-malignant origin, being a multidimensional experience requiring multimodal therapy.

Forty-five of 51 patients (88%) completed questionnaires. Their mean (range) age was 53.9 (31–76) yr and mean (range) duration of pain complaint 13.7 (4–35) yr. The duration of pump implant

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was mean 3.7 (range 0.5–9.1) yr. All patients received diamorphine. Other drugs used were bupivacaine (33), clonidine (33) and baclofen (13). Adjuvant analgesics were used more commonly in those with a neuropathic component to their pain compared with those with nociceptive pain (29 of 31 with neuropathic/mixed neuropathic-nociceptive pain compared with 9 of 20 with nociceptive pain) and were introduced if pain relief was not achieved with diamorphine alone.

Pain reduced from a mean (SD) of 8.9 (1.2) before implant to 5.3 (2.3) after implant ($P<0.001$, paired t-test for samples of unequal variance). A range of quality of life measures assessing the physical, psychological and sociological dimensions of pain experience were also significantly improved. There was no significant difference in outcome scores between neuropathic and nociceptive diagnoses. The mean dose of diamorphine was less in the nociceptive group being 2.3, 3.4 and 4.3 mg day^{-1} at 1, 2 and 3 yr post-implant compared with 3.1, 5.2 and 5.3 mg day^{-1} in the neuropathic group ($P<0.05$, 2-way ANOVA).

Within the limits of retrospective design, intrathecal implantable drug delivery of diamorphine with the opportunity to add bupivacaine, clonidine or baclofen or combinations thereof have a reasonable long term yield upon pain and quality of life in chronic pain of non-malignant origin.

Keywords: pain, chronic; infusions, intrathecal

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The effect of propofol on subcortical somatosensory evoked responses

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This study investigated the effect of propofol on the P_{15}-N_{20}, N_{20}-P_{25} and P_{25}-N_{35} amplitudes of the somatosensory evoked response (SER). These amplitudes are thought to represent activity in the pons/thalamus, thalamus/primary sensory cortex, and sensory cortex respectively.[1] Previous work using desflurane[2] and sevoflurane[3] revealed an unexpected increase in P_{15}-N_{20} amplitude with increasing anaesthetic depth. Propofol is an intravenous anaesthetic with very different physicochemical properties to the volatile agents. The study was designed to assess if this increase in activity was reproducible with propofol during single agent anaesthesia.

Twelve ASA I or II patients aged 18–61 were recruited. Following induction with propofol using the Diprifusor™ total intravenous anaesthesia (TIVA) pump, vecuronium 0.1 mg kg^{-1} was given and the subjects were ventilated to normocapnoea via a laryngeal mask airway. Each patient was randomized to sequentially increasing or decreasing concentrations of propofol, and this was administered during 5 steady state periods within a predicted plasma concentration range of 2.5–14.8 μg ml^{-1} blood. The median nerve was stimulated at the wrist with an electrical pulse delivered at a rate of 2.2 s^{-1}, and at an intensity above the motor threshold. The SER was derived from the electroencephalogram (EEG) and recorded using electrodes at Fz and $C_{3'}$. SER data corresponding to the last 2.6 min of each 15 min concentration level (1024 EEG sweeps) were log transformed and analysed offline.

There were no significant differences between the ascending and descending subgroups ($P=0.22$). The amplitudes N_{20}-P_{25} and P_{25}-N_{35} fell with increasing plasma propofol concentration ($P<0.001$ in each case). For the amplitude P_{15}-N_{20}, quadratic regression lines provided a better fit for all the patients' data than straight lines ($P<0.001$). The point of maximum amplitude was found at a mean propofol concentration of 9.2 μg ml^{-1} blood (95% confidence interval 8.3–10.0 μg ml^{-1} blood).

These data indicate that the changes in P_{15}-N_{20} amplitude are consistent across a range of anaesthetic agents with differing pharmacological properties. The cause of this signal potentiation is not known but we speculate that it could be due to an increase in midbrain inhibitory potentials or increased gamma wave activity secondary to decreased $GABA_A$ receptor inhibition of interneurons.[4] The decrease in activity with increasing agent concentration in the N_{20}-P_{25} and P_{25}-N_{35} amplitudes is as one would predict from studies of other evoked response and EEG variables.[1]

Keywords: nerves, evoked potentials; anaesthetics i.v., propofol

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The actigraphic assessment of circadian rhythm following general anaesthesia

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Normal sleep patterns follow a daily circadian rhythm. The effect of anaesthesia on this rhythmicity is not well documented. We wished to study the effect of general anaesthesia on sleep patterns. Actigraphy is the study of sleep via movement, and has been validated in the assessment of circadian rhythm.[1 2] A wristwatch, containing a small accelerometer and data logger, is worn on the patient's non-dominant arm. Frequency and amplitude of movement are recorded at 1-min intervals throughout the observation period. It can be worn for several weeks at a time and monitors sleep in the home environment, reducing the impact of 'first-night' effects seen in laboratory assessments of sleep.[3] Data is processed using Non-Parametric Circadian Rhythm analysis software (Cambridge Neurotechnology®). A key feature of this analysis is the Interdaily Stability Score (IS). This provides information on how close the patient's sleep pattern is to a normal circadian pattern. A value of 1.0 suggests a true circadian pattern whereas a value of 0 indicates a random sleep pattern.

We studied 13 adult subjects, 5 volunteers (no anaesthesia), 5 day-case patients and 3 gynaecological patients scheduled for laparotomy. Patients were interviewed 1 week prior to anaesthesia. Following written informed consent they were asked to wear the monitor for 1 week before their operation and for 4 weeks afterwards. Patients also kept a basic sleep diary. Volunteers wore the monitor for a 5-week period. Patients with diagnosed sleep problems, depression or on sedative medications were excluded. Data were analysed using SPSS v8.0. IS scores were analysed using ANOVA.

The 'watch' was well tolerated in all groups. IS scores were altered significantly in the laparotomy group. This was most evident in the first week following operation. A biphasic sleep pattern was seen in a number of patients following general anaesthesia, lasting from 7 to 28 days (Table 2).

Table 2 Numbers expressing biphasic sleep pattern and Intradaily Stability (IS) scores before surgery and for 4 weeks after surgery expressed as mean (SD). †Within group comparison, *between group comparison, all values $P<0.02$

	Biphasic pattern						
	Yes	**No**	**IS Pre**	**IS Post 1**	**IS Post 2**	**IS Post 3**	**IS Post 4**
Control	0	5	0.68 (0.04)	0.67 (0.09)	0.69 (0.02)	0.68 (0.09)	0.66 (0.01)
Minor	2	3	0.57 (0.17)	0.49 (0.12)	0.57 (0.13)	0.57 (0.10)	0.46 (0.05)
Major	3	0	0.68 (0.02)	0.34†* (0.20)	0.59 (0.10)	0.67 (0.06)	0.65 (0.08)

This pilot study would imply that general anaesthesia induces an alteration in sleep pattern, especially after a major procedure, which can persist for up to 28 days. Further work is required to establish the clinical significance of this finding.

Keywords: sleep, circadian rhythm; anaesthesia, general

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Bispectral index during isoflurane or sevoflurane anaesthesia in children

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Bispectral Index (BIS) falls with increasing depth of anaesthesia, reflecting a reduction in global brain metabolism in adults.[1 2] There has been one study of BIS in children and neonates,[3] using sevoflurane anaesthesia blinded to the anaesthetist. The objective of this study was to evaluate the utility of BIS for tracking anaesthetic progress with BIS visible during unrestricted isoflurane or sevoflurane anaesthesia.

Children (n=16, ASA I or II) scheduled for elective minor surgery were recruited. The mean age was 2 yr, 4 months (range 1 month to 6 yr). Initial maintenance anaesthesia was with isoflurane (n=11) or sevoflurane (n=5) in N_2O/O_2. Eight patients breathed spontaneously, and 8 were subject to IPPV. A standard commercial BIS monitor (v3.3 A1050 with Sensor electrode montage, Aspect Medical) was connected to a laptop PC to enable archiving of data.

BIS was found to reduce during increasing depth of anaesthesia in all subjects in a similar profile to that expected from routine use of BIS in adults. There was no correlation between age and the distribution of BIS observed during anaesthesia. A rapid increase in BIS was observed in one patient subject to IPPV (Figure 1). This was traced to a faulty isoflurane vaporiser. BIS reduced rapidly after substitution with a sevoflurane vaporiser. It is likely that BIS prevented a case of awareness in this subject. It was expected that BIS would not be measurable in the youngest children, and would become an emergent feature of development, so the presence of adult-like BIS in even the youngest subjects was surprising. Future studies should examine whether BIS is a useful index in premature neonates.

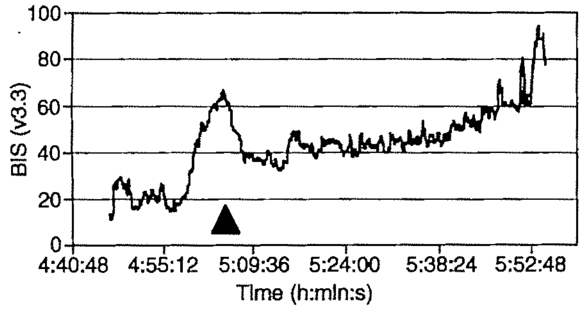

Fig 1 BIS during failure of isoflurane vaporiser (subject age=2 yr, 1 month). Mark=substitution with sevoflurane.

Keywords: monitoring, EEG; anaesthesia; children

Acknowledgement

We gratefully acknowledge the loan of an A1050 monitor from Aspect Medical Systems.

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Manual versus target-controlled infusions of propofol: propofol dosage and BIS scores

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Although propofol infusions for maintenance of anaesthesia can be administered using manual infusion regimens, the use of Target Controlled Infusion systems (TCI), which are based on pharmacokinetic models, allows better control and ease of administration. However, the use of TCI systems has been shown to result in administration of higher doses of propofol which may result in somewhat delayed recovery.[1 2] The aim of the present study was to investigate if this was due to difference in the depth of hypnosis with the two systems of administration.

Fifty ASA grade I–III adult patients undergoing elective orthopaedic surgery lasting 30 min or more were allocated randomly to manual or TCI propofol infusion regimens for maintenance of anaesthesia. All patients received fentanyl $1.5\ \mu g\ kg^{-1}$ at induction. Patients in the manual group received propofol $1\ mg\ kg^{-1}$ followed by an infusion at $10\ mg\ kg^{-1}\ h^{-1}$, reduced to 8 and $6\ mg\ kg^{-1}\ h^{-1}$ at 10 min intervals. In the TCI group the starting target concentration was $5–6\ \mu g\ ml^{-1}$ followed by maintenance at required levels. Further adjustments in propofol dosage were made as required. The airway was maintained using a laryngeal mask and patients' lungs ventilated with nitrous oxide 65% in oxygen. Adequacy of anaesthesia in both groups was based on absence of sweating, lacrimation or movement, and stable haemodynamics. All patients received morphine 0.1 mg

Table 3 Maintenance infusion dose (mg kg^{-1} h^{-1}) of propofol used and BIS scores (mean and SD) for first 60 min. *$P<0.05$, **$P=0.056$ compared to manual group

	10 min	20 min	30 min	40 min	50 min	60 min
Propofol dose						
Manual	9.0 (1.6)	8.3 (1.2)	6.3 (1.0)	6.0 (0.9)	6.1 (1.2)	6.1 (1.8)
TCI	12.9 (3.2)*	9.5 (2.2)*	7.8 (2.2)*	6.6 (2.0)	6.7 (2.0)	6.4 (2.3)
BIS scores						
Manual	47 (11)	44 (9)	48 (10)	49 (9)	48 (9)	47 (10)
TCI	37 (9)*	40 (9)**	46 (13)	46 (11)	49(14)	48(13)

kg^{-1} 15 min before the anticipated end of surgery. BIS scores were recorded by an observer not involved in administration of anaesthesia, with the administering anaesthetist being unaware of the BIS scores. The dose of propofol administered was recorded along with recovery times. Data were analysed using Student's *t* tests.

The groups were similar with regard to age, weight, and duration of anaesthesia. The total dose of propofol (mean (SD)) used in the TCI group was significantly higher (8.1 (1.03) *vs* 9.9 (1.64) mg kg^{-1} h^{-1}) being mainly due to significantly higher dosage for the first 30 min (Table 3). However, there was no significant difference in the recovery times. The BIS scores were also lower in the TCI group in the first 15 min. In conclusion, propofol administration by a TCI system results in the administration of higher doses mainly due to higher rates in the initial period.

Keywords: anaesthesia i.v., propofol; infusions, i.v.

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Cerebral blood flow as measured by MRI during changes in end-tidal CO_2 partial pressure

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Magnetic resonance imaging (MRI) is being used increasingly to assess intracerebral haemodynamics including cerebral blood flow (CBF). In this study we aimed to examine the sensitivity of MRI in detecting the changes in CBF during changes in end-tidal CO_2 partial pressure (PE'_{CO_2}).

Twelve healthy male volunteers (mean age 35 yr) were studied in the supine position. CO_2 reactivity of the cerebral vessels was confirmed by using transcranial Doppler ultrasonography (TCD). Continuous recording of blood flow velocity in the right middle cerebral artery (V_{MCA}) was established. A close fitting anaesthetic facemask (BOC type) was used and a Bain anaesthetic breathing system and PE'_{CO_2} monitoring were attached. V_{MCA} and corresponding PE'_{CO_2} were recorded at baseline and at corrected 1.0 kPa below (voluntary hyperventilation) and corrected 1.0 kPa above (rebreathing) the baseline value. The subject was then placed in the MRI scanner. A single slice contrast enhanced T_1 weighted dynamic perfusion technique was used. A bolus of 1.5 ml of Gadolinium-diethylene triamine penta-acetic acid (Gd DTPA) followed by 8.5 ml of saline was injected in less than three seconds. One brain and one neck image were acquired every 3 s. The brain slice was positioned parallel to the floor of the frontal fossa just below the corpus callosum. Imaging was performed on a 1.5 T MRI scanner (Siemens Vision), cerebral blood flow (CBF) parametric images were produced and the right MCA territory defined to allow derivation of mean flow.[1] These measurements were made at baseline PE'_{CO_2} and then repeated at 1kPa above and 1 kPa below the baseline as for the TCD study. An investigator blinded to the subjects' PE'_{CO_2} examined the CBF measurements and excluded data if movement artefacts were present.

Table 4

	Hypocapnia (1 kPa < baseline)	Baseline	Hypercapnia (1 kPa > baseline)
V_{MCA} (cm s^{-1})	37.1	52.8	68.3
(SD)	(10.3)	(9.7)	(16.2)
n	12	12	12
CBF (ml 100 g^{-1} min^{-1})	30.5	37.0	47.1
(SD)	(7.4)	(8.2)	(9.2)
n	6	9	7

Of the 12 subjects studied no MRI blood flow data were interpretable in three subjects. CBF data for both hypo and hypercapnia were analysable for four subjects and in the remaining five subjects only either hypo- or hypercapnic data were usable. The sensitivity of the usable data from MRI was 85% (Table 4).

In a small sample MRI provided a sensitive method of assessing changes in CBF to a 1kPa change in PE'_{CO_2}. However, 45% of the data obtained was unusable and the technique needs to be refined further before MRI can be used to assess changes in cerebral blood flow consistently in clinical or research settings.

Keywords: blood, flow, cerebral; monitoring, magnetic resonance imaging

Acknowledgement

Support from The Special Trustees for Nottingham University Hospitals.

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Plasma lidocaine levels following insertion of 2% lidocaine gel into the uterine cavity after thermal ablation

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Intra uterine balloon thermal ablation is a technique used to treat menorrhagia. A number of different anaesthetic techniques ranging from sedation to general anaesthesia with or without local or regional anaesthesia have been used[1] for this procedure. We hypothesized that intrauterine application of 2% lidocaine gel

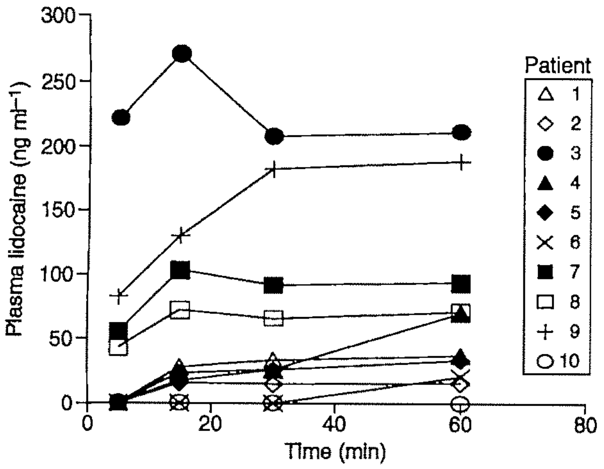

Fig 2 Lidocaine plasma concentrations for each patient after intra-uterine application of 2% lidocaine gel.

may reduce postoperative pain. We first wished to establish how much lidocaine is absorbed systemically from the uterine cavity after thermal ablation.

Ten ASA I–II patients (age 20–50 yr) underwent uterine thermal ablation under general anaesthesia. They each had 11 ml of 2% lidocaine gel (Instillagel^{TM}) inserted into the uterine cavity at the end of the procedure. Blood samples were taken at 5, 15, 30 and 60 min after insertion and analysed using high pressure liquid chromatography.

Mean (range) plasma lidocaine concentrations at 5, 15, 30 and 60 min were 40.3 (0–221.9) ng ml^{-1}, 66.3 (0–271.9) ng ml^{-1}, 64.9 (0–208) ng ml^{-1}, and 75 (0–212) ng ml^{-1} respectively (Figure 2).

There was minimal systemic absorption of lidocaine from the uterus following uterine thermal ablation, measured levels were well below the toxic plasma levels for lidocaine (5 µg ml^{-1}).[2]

Keywords: anaesthetics local, lidocaine; pharmacokinetics, intrauterine

Acknowlegements

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Breath interval, inspiration time and tidal volume to compare repeat doses of alfentanil i.v. during spontaneous ventilation

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Previously, breath interval after alfentanil 2.25 µg kg^{-1} gave a dynamic elimination half life of 5.04 (2.9) min and mean effect residence time of 7.0 (3.4) min.[1] We have used breath interval (Tt), inspiration time (Ti), inspired tidal volume (Vt) and derived indices[2] to compare the dynamic effects of two doses of alfentanil in the same patient.

Patients admitted for knee arthroplasty were studied. Anaesthesia was induced with propofol and maintained with 0.8% isoflurane and 67% N_2O in oxygen though a laryngeal mask. Sciatic and 3-in-1 femoral blocks were performed. A Capnomac Ultima (Datex) measured gas flow at the laryngeal mask. The analogue output was digitized at 100 Hz and recorded. Change of direction of flow timed the beginning and end of each inspiration and expiration. Vt was logged every 10 s from the serial output. Alfentanil 2.5 µg kg^{-1} was given i.v. 5 and 25 min after surgery began.

Twenty-two patients were studied, 11 were male. They were aged 66 (range 29–89) yr, weighed 77 (13) kg with height 171 (10) cm (mean (SD)). Mean effect residence time after alfentanil 1st dose was 6.6 (2.1) min and 2nd dose 8.1 (3.8) min, P=0.02. Alfentanil increased Tt, Ti, Vt and mean inspiratory flow (Vt/Ti). Inspiratory duty cycle (Ti/Tt) was decreased (Table 5).

The time to peak Tt effect was: 1st dose 3.4 (1.8) min and 2nd dose 3.1 (1.5) min, was significantly shorter (P=0.0001) than both time to peak Ti: 1st dose 8.0 (3.0) min and 2nd dose 7.4 (2.8) min, and time to peak Vt: 1st dose 8.5 (3.4) min and 2nd dose 8.4 (4.9) min. There were no differences between times to peak Ti and peak Vt for either dose of alfentanil.

Second doses of alfentanil have a longer duration of dynamic effect than the first dose. Changes in Ti and Vt are likely to be consequent to the increased expiration time (Te) due to alfentanil. The rise in Vt obtained with regional block is opposite to results obtained without regional block.[3]

Keywords: anaesthetics i.v., alfentanil; ventilation, spontaneous

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Table 5 Effect of alfentamil on Tt, Ti, Vt, Vt/Ti and Ti/Tt. Mean (SD), n=22

	Base	Peak1	Peak1-base	*P*	Peak2	Peak2-base	*P*	Peak2-Peak1	*P*
Tt (s)	3.1 (0.8)	8.2 (5.1)	5.1 (4.7)	0.0001	9.0 (5.2)	5.9 (4.8)	0.0001	0.8 (2.4)	NS
Ti (s)	1.0 (0.3)	1.3 (0.3)	0.3 (0.1)	0.0001	1.3 (0.3)	0.3 (0.1)	0.0001	0.03 (0.1)	NS
Vt (ml)	313 (72)	485 (175)	172 (170)	0.0001	504 (167)	191 (153)	0.0001	19 (184)	NS
Vt/Ti (ml.s^{-1})	318 (55)	391 (151)	73 (130)	0.007	390 (98)	72 (93)	0.0005	-1.3 (141)	NS
Ti/Tt	0.32 (0.05)	0.18 (0.08)	–0.14 (0.07)	0.0001	0.16 (0.08)	–0.17 (0.08)	0.0001	–0.017 (0.03)	0.02

Motor cycle injury and mortality: implications for anaesthetists

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The implementation of ATLS protocols and a better understanding of the pathophysiology of injury have implications for improved care of trauma patients. We have recently introduced a consultant-lead trauma team in our hospital. The present study examines all motor cycle accident injuries presenting in our region 1993 to present date, to assess the impact of these factors on mortality.

Data were collected in electronic format on all motorcyclists and pillion passengers presenting to trauma units in Yorkshire following a road traffic accident. The database was opened in January 1993 and remains current. Data includes injury severity score (ISS), demographic details, clinical details, therapeutic and resuscitation data, and personnel treating the patient. All patients received initial resuscitation according to ATLS protocols, and where operative surgery was required this was undertaken within 24 h of hospital admission. Duration of hospital stay and mortality were recorded.

Data were collected on 1239 patients, 1120 male and 119 female. Mean age was 30.7 yr (22–36 yr interquartile range). Mean ISS was 13.2 (9–14). This remained constant throughout the study period. Fluid resuscitation in the emergency room was 688 ml (0–1000 ml) and blood transfused was 0.26 units (0.18–0.34, 95% confidence interval). 10% of patients did not wear a crash helmet. This group were over-represented in those with impaired Glasgow Coma Score, P=0.0007, Chi square, although there was no increased mortality in those without helmets. Overall, 74 patients died (6.0%, 4.7–7.3%, 95% CI). Factors apparently associated with survival were entered in a logistic regression model. Factors independently associated with survival were: transfusion requirement in the emergency room (odds ratio 0.8, 0.6–1.06 95% CI), being treated more recently (days into programme) (OR 1.001, 1.0003–1.002); senior anaesthetist – consultant or senior registrar *vs* junior (4.04, 1.19–13.7) and ISS (0.85, 0.82–0.89). Age, gender, grade of surgeon and involvement of the trauma team were apparently unimportant.

Our study represents a large group of patients sustaining major trauma from motor cycle accidents. The age of the accident victims was greater than expected. Head injury but not mortality was reduced by the wearing of helmets. The data confirmed our impression that trauma management has improved over time. The single factor most likely to have a major impact on survival was the involvement of a senior anaesthetist, and this exceeded the effect of senior surgical input or the involvement of a trauma team. This finding has major implications for the way anaesthetic input into trauma services should be organized.

Keywords: anaesthesia, audit

Pilot tubes: to snap or not to snap

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The incidence of respiratory complications associated with tracheal extubation may be higher than that during intubation. The causes of these complications are diverse, but difficulty in removing the endotracheal tube has been reported as potentially life threatening. The most common cause of difficult extubation is failure to deflate the endotracheal tube cuff. It is believed that the practice of snapping of the pilot tube in order to deflate the cuff can cause the cuff to deflate slowly and unpredictably. In some cases the cuff has failed to deflate at all. There are few who would advocate extubating patients without deflating the cuff, but by snapping the pilot tube, there is a risk of doing that.

A bench test was carried out to determine whether deflation by snapping the pilot cuff was significantly slower, and less predictable than deflaton using a syringe. A model trachea was developed, and constructed. Endotracheal tubes were introduced into the model, and inflated, using a syringe, with 8 ml of air. A weight was attached so that when the cuff was deflated, the weight would cause the endotracheal tube to fall out of the model trachea. The weight would then strike a plate switch which turned off the timer (which had been started manually). A total of 80 tubes were tested; 40 were deflated using a syringe, and 40 deflated by snapping of the pilot tube. The times for deflation using a syringe ranged from 0.33 s to 0.76 s, with a mean deflation time of 0.519

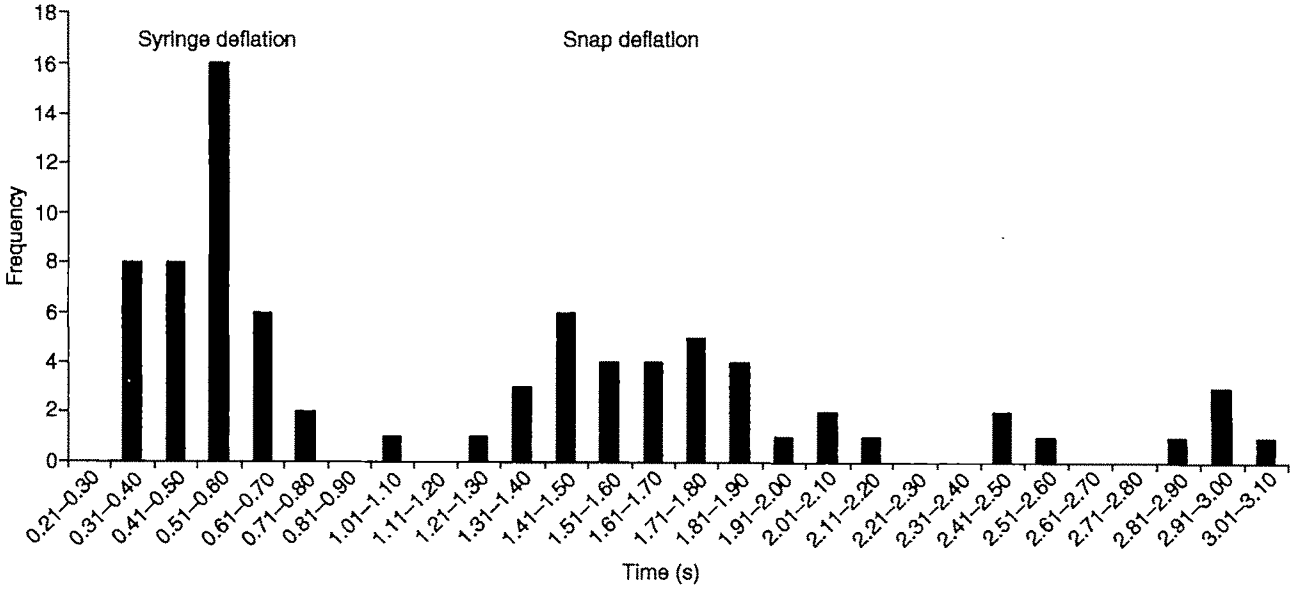

Fig 3 Bench model data.

s. (SD 0.115) (Figure 3). The times for snap deflation ranged from 1.06 s to 3.02 s with a mean deflation time of 1.868 s. (SD 0.522). The difference was highly significant ($P<0.001$). The wide time distribution in the snap group implies a less predictable as well as slower deflation. Where rapid cuff deflation is important, snapping the cuff is inferior to syringe deflation.

Keywords: intubation, tracheal; complication, intubation tracheal

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Thromboelastography: validation of TEG 3000® and TEG 5000®

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Thromboelastography (TEG®) has been used as a monitor of whole blood coagulation in a variety of clinical settings.[1] The equipment is sensitive and it is recommended that reference intervals are determined for individual machines.[2] A comparison of TEG® machines has not been formally performed. The aim of this study was to assess the agreement between the channels of the TEG 3000® and the recently introduced TEG 5000® (Haemoscope Corp. Illinois, USA).

We recruited 25 healthy volunteers and recorded native whole blood TEG® variables in all four channels simultaneously in accordance with manufacturers' recommendations.[2] The sequence in which channels were loaded was rotated systematically. The analysis was repeated using Celite® activated samples.[2] Agreement was assessed using intraclass correlation coefficients (r_i) for channels within and between machines, by repeated measures analysis of variance (RMANOVA), Bland-Altman plots and coefficients of variation (CV).

The results for the four TEG® variables are reported as r_i (Table 6). The best agreements were for α angle and maximum amplitude (MA). For Celite® activated samples there were small but statistically significant differences ($P<0.05$) between the two machines indicating quicker and stronger clot formation in the TEG 5000®. This might be due to interaction of Celite® with liquid paraffin on the TEG 3000® samples. Using Bland-Altman plots, there was considerably wider variability for *r* distance (CV 0.20–0.30) compared to MA (CV 0.03–0.09), irrespective of Celite® activation.

Agreement assessed by r_i: <0.40 as poor, 0.41–0.60 as moderate, 0.61–0.80 as good, >0.8 as excellent.

Both TEG® machines provide more consistent results with native blood. There are clear differences between machines when using Celite®. The agreement within and between machines is consistently more reliable for MA than for *r* and *k* distance. We recommend that users validate their own machines in a similar manner.

Keywords: blood, coagulation; measurement techniques, thromboelastography

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Enoxaparin 20 mg or 40 mg as perioperative prophylaxis

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Low molecular weight heparin (LMWH) is a recommended method of prophylaxis against venous thromboembolism. Unlike unfractionated heparin, it is not readily monitored by the activated partial thromboplastin test (aPTT), but requires a more complex assessment of anti factor Xa activity.[1] This study examined the effect of two doses of enoxaparin on anti factor Xa activity over 24 h.

Twenty women, ASA Class I or II, scheduled for elective hysterectomy, were allocated randomly to receive enoxaparin 20 mg or 40 mg on the day before their operation. Observers were blind to the dose received. Serial venous blood samples were taken before injection (9 am) and at 1, 2, 4, 6, 8,12 and 24 h after injection. Anti factor Xa activity was measured using the Coatest assay (Chromogenix). Laboratory reference intervals give the therapeutic range for anti factor Xa activity as 0.2–0.4 u ml^{-1}. Statistical analysis was carried out using Microsoft Excel 2000, SPSS for Windows 7.0, and GraphPad Prism 3.0. Personal characteristics are expressed as means (SD) and comparisons are made using Student's *t* test and Pearson correlation as appropriate.

There were no clinical differences between groups (Table 7). Personal characteristics are shown as mean (SD) and count.

Table 6 Agreement in channels within and across machines as assessed by r_i. *P* values for differences across TEG 3000® and TEG 5000® as assessed by RMANOVA * <0.05, ** <0.0001

	Within TEG 3000®		**Within TEG 5000®**		**Between machines**	
	Native	**Celite®**	**Native**	**Celite®**	**Native**	**Celite®**
r	0.70	0.71	0.63	0.75	0.54	0.76
k	0.75	0.60	0.43	0.57	0.66	0.58*
α angle	0.90	0.58	0.73	0.54	0.82	0.58**
Maximum amplitude (MA)	0.91	0.81	0.86	0.72	0.87	0.67**

Table 7 Demographic data and hormonal status

Dose (n=10)	**Age (yr)**	**Height (cm)**	**Weight (kg)**	**Menopause**			**Hormonal supplement**
				Pre	**Peri**	**Post**	
20 mg	45.1 (5.3)	160.8 (8.1)	70.3 (13.9)	5	3	2	0
40 mg	46.7 (10.6)	162.2 (7.4)	73.1 (15.0)	4	4	2	1

After 40 mg, area under the curve of anti Xa activity (units $h^{-1}\,ml^{-1}$) was greater than after 20 mg, 4.51 *vs* 2.42, (95% confidence interval (CI) difference 0.13–4.05), (P=0.038). The time after injection at which anti Xa activity passed below the therapeutic range (0.2 $u\,ml^{-1}$) was 6.1 h after 20 mg, and 10.8 h after 40 mg, (95% CI difference 0.22–9.33), (P=0.041). Pearson correlation between the dose of enoxaparin (mg kg^{-1}) and the time to return to less than 0.2 $u\,ml^{-1}$ was 0.45 (P<0.05).

Anti factor Xa analysis shows that the effect of doubling the dose of enoxaparin from 20 mg is largely to increase and prolong the peak effect, with significantly more time within the therapeutic range. Individual variability is large and makes identification of a best mg kg^{-1} dose uncertain.

Keywords: complications, thromboembolism; blood, anticoagulants, heparin

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Use of the platelet function analyser (PFA-100) in pregnancy

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The ability to arrest bleeding from a small puncture to a blood vessel, as may occur during epidural insertion, is mainly a function of primary haemostasis, the formation of a platelet plug. The PFA-100, a new automated platelet function analyser which simulates this reaction under high shear conditions,[1] is becoming increasingly popular as a rapid bench-top assessment of primary haemostasis. It measures the time, Closure Time (CT) in seconds, taken by a citrated whole blood sample to occlude a microscopic aperture in a membrane by forming a platelet plug. The test could prove to be a convenient assessment of platelet function prior to regional anaesthesia when impaired haemostatic capacity is suspected. The preliminary aim of this study was to establish a 95% reference range for CT values within our local healthy pregnant population prior to assessing its value in high risk pregnancies with impaired platelet function.

Whole blood samples obtained at the time of intravenous cannulation from 40 healthy women presenting for elective Caesarean section were collected in 105 mmol $litre^{-1}$, 3.2% buffered sodium citrate syringes (Sarstedt Monovettte®). Patients with known bleeding diatheses, pre-eclampsia, gestational thrombocytopaenia or receiving anticoagulant or antiplatelet medication were excluded. An 800 µl citrated blood sample from each syringe was then transferred into a PFA-100_{epi} test cartridge containing a collagen membrane with epinephrine acting as a platelet activator. The CT for each blood sample was then automatically analysed by the PFA-100. Statistical analysis included the Kolmogorov-Smirnov normality test and standard error of the mean (SE) (P<0.05).

The coefficient of variation (CV) for the PFA-100 was previously estimated as <10%. The mean (SD) platelet count and haematocrit for our patient sample was 250.03 (78.98)×10^9 $litre^{-1}$ and 35.20 (3.00)% respectively. Data for CT were normally distributed (P=0.98). The 95% reference range for the CT and 95% confidence intervals (CI) for both its upper and lower limits were calculated from the mean (1.96 SD) and limit (1.96 SE) respectively (Table 8).

Table 8 Closure times

	Closure time (s) (n=40)
Mean (SD)	103.38 (18.79)
95% Reference range	66.50–140.22
95% CI for lower; upper limits	56.54–76.46 ; 130.26–150.18

The upper limit of the CT reference range in the pregnant population within its 95% CI may indicate impaired haemostasis and can potentially provide guidance to anaesthetists considering regional anaesthesia in the high risk parturient with suspected platelet dysfunction. The PFA-100 could prove to be a useful tool in the rapid assessment of primary haemostasis before regional blockade is attempted in patients with disorders such as pre-eclampsia and gestational thrombocytopaenia.

Keywords: blood, platelets; pregnancy

Acknowledgements

Funding from an Obstetric Anaesthetists' Association research grant; Research Fellowship funding (JRD) from SIMS Portex Ltd.

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National Obstetric Anaesthetic Database (NOAD): results of 1999 survey of post-delivery headaches

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Post dural puncture headaches (PDPH) are a recognized complication of extradural and spinal blockade in obstetrics. The incidence, diagnosis and management of PDPH vary between maternity units.[1–3] This prospective national survey aimed to measure the severity and clinical management of all significant headaches (continuous or intermittent headache >6 h) presenting in postpartum women using monthly collection of data from participating units.

Although all 260 maternity units in the UK were invited to participate during 1999, a pilot survey identified that only 110 audited PDPH. There were two types of data collection: (1) a composite monthly return [data 1] tabulating the numbers of different analgesia/anaesthetic techniques used per patient, headaches and their severity, dural taps and epidural blood patches and (2) individual anonymous clinical records of headaches [data 2] to support the aggregated [data 1] record. A verbal rating scale scored postpartum headaches as mild, moderate or severe.

From 93 centres[$] submitting data, the majority of women (64 244 out of 65 348) had a single anaesthetic intervention (epidural 38 271 (60%); spinal 16 844 (26%); combined spinal epidural [CSE] 4926 (8%); general anaesthesia 4203 (7%)). Following anaesthetic intervention, 1127 headaches were reported in data 1 and 976 in data 2 (Table 9). Headaches within a group of women without anaesthetic intervention (609 [data 1] and 536 [data 2]) were included for comparison. Results from data 2 included 398 diagnosed PDPH. The choice of blood patch for PDPH management depended on headache severity, such that 86% (171/199) of severe PDPH were treated with a blood patch.

Table 9 Based on data 2, the numbers of women experiencing headache (mild, moderate or severe) after a single or no anaesthetic technique (dural tap for single technique in brackets)

Technique	Mild headache	Moderate headache	Severe headache	Total
Epidural only	200 (19)	153 (39)	155 (80)	508 (138)
CSE only	29	26	18	73
Spinal only	106	107	52	265
None	29	5	1	35

The total number of blood patches performed was 249. Despite the infrequent use of opioids in 17% (33/199) of severe PDPH, the first blood patch in severe PDPH was given 24–48 h after delivery in 22% (37/171) and in 65% (112/171) >48 h later.

Aggressive management of PDPH by blood patch thus depends on headache severity. In this context the lack of analgesia and delay in blood patching are surprising. Whether this reticence arises from mothers or anaesthetists is uncertain.

Keywords: anaesthesia, obstetric; anaesthesia, audit

Acknowledgement

We thank the Obstetric Anaesthetists' Association for funding.[$] A list of participating members or centres (i.e. one or more maternity units) is available from the authors.

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Analysis of maternal age and social class on risk of obstetric intervention and obstetric anaesthetic requirements

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Women having their first baby at an older age are at increased risk of obstetric intervention and are therefore prone to more obstetric anaesthetic input.[1] It has also been shown that women in higher social classes have increased risk of obstetric intervention.[2]

The Cardiff Births Survey data-base holds details of all deliveries in Cardiff and The Vale of Glamorgan. Women of all social classes deliver in one of two units that share obstetric and anaesthetic staff. The 1–3:4–6 ratio of social classes in Cardiff and the Vale of Glamorgan is 55.6%:39.0% *vs* 51.1%:44.6% in England and Wales as a whole, with ethinc populations of 4.8% *vs* 5.9%. Data on all deliveries in the two units 1990–1998 were examined. Of the 13452 women in their first labour with an uncomplicated obstetric and medical history, the 10721 who had been allocated a social class were analysed.

In social classes 1 to 6, the percentages of patients requiring instrumental delivery (ID) (Caesarean or instrumental vaginal), were 47.8, 44.4, 41.6, 37.8, 34.3, 31.3; with mean ages 30.3, 29.0, 26.7, 25.4, 23.9, 22.1 (Figure 4). The percentages requiring ID in age groups 15-, 20-, 25-, 30-, 35- were 25.2, 33.0, 41.5, 50.9, 59.2. The dependence of ID on social class and age group was analysed by logistic regression. Social class was a highly significant predictor of outcome (χ^2=84 with 1 df, P<<0.001), but age group alone was much better (χ^2=397, 1df); adding social class then had a negligible effect: χ^2=2.2, 1 df, P>0.1. Thus virtually all the differences in ID between social classes can be accounted for in terms of age. Even treating age group and social class as ordinal categorical predictors, produced no appreciable improvement: P>0.75. The dependence of the probability, p, of ID on age was obtained by treating each patient as a separate trial, with outcome of 0 or 1, yielding $p = e^z/(1+e^z)$ where $z=-2.468+0.07739\times$age. Applying this to the mean age of each social class led to Figure 4.

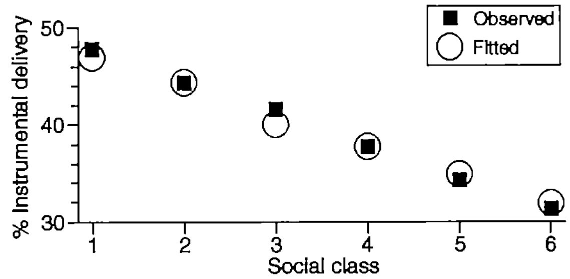

Fig 4 Instrumental delivery as a function of social class.

Use of epidural anaesthesia in labour showed a similar but lesser variation with age (33.8% to 47.1%) and social class (42.6% to 32.3%), the latter again explicable in terms of age.

These data demonstrate that there is an increasing risk of obstetric intervention and anaesthetic requirement throughout the mother's twenties and into her thirties. Small differences between maternity units in average age of mothers in their first pregnancy could have dramatic effects on obstetric intervention rates. Social class of the local population will also affect average maternal age. The old adage of 'too posh to push' should now be changed to 'too old to avoid obstetric intervention'.

Keywords: anaesthesia, obstetric; anaesthesia, audit

Acknowledgement

Thanks to the Cardiff Births Survey for allowing us access to the data.

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Neuromuscular monitoring in the critically ill: milliamperage requirements for supramaximal stimulus

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A stimulating current of 50–60 mA has been recommended to produce a maximal muscle response when neuromuscular monitoring is carried out during anaesthesia.[1] Intensive care (ICU) patients commonly develop peripheral oedema which may affect supramaximal current requirements. The aim of this study was to

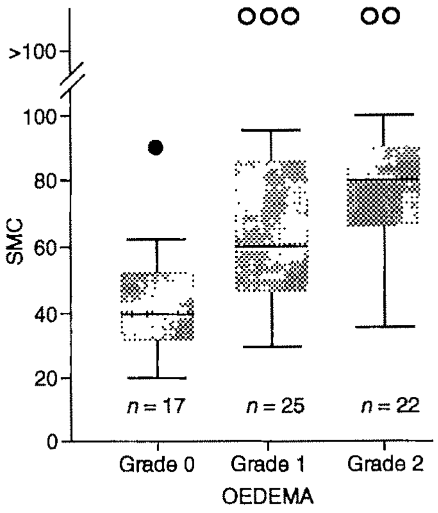

Fig 5 Milliamperage requirement for ICU patients.

investigate the effect of oedema on the current required to elicit a supramaximal stimulus at the first dorsal interosseous muscle.

The neuromatic 2000 electromyograph (Dantec®) was used. The severity of oedema was graded by the same blinded observer. Grade 0 represented no oedema, grade 1 mild oedema and grade 2 gross oedema. The skin was prepared with acetone and stimulating electrodes were placed over the ulnar nerve; the sensing electrode was placed over the first dorsal interosseous muscle. The stimulating current was increased in 5 mA increments to a maximum delivered current of 100 mA. The magnitude of the recorded electromyographic response was measured. The supramaximal stimulus was that stimulus above which no further increase in EMG amplitude was gained. Hand dominance, core-periphery temperature gradient and the presence of sepsis were documented.

Seventeen patients had no oedema (grade 0), 25 had moderate oedema (grade 1) and 22 had grade 2 oedema. Median supramaximal current (SMC) was 40 mA in grade 0, 60 mA in grade 1 and 82.5mA in grade 2 oedema (Figure 5). 100 milliamps was insufficient to elicit a supramaximal response in five patients. These differences were found to be statistically significant between all groups $P<0.001$ (Kruskal-Wallis test). The application of pressure decreased the current requirements in grade 1 and grade 2 oedema but made no difference in patients with no oedema.

Plasma electrolyte, dominance, core-periphery temperature gradient and sepsis did not effect the SMC. Supramaximal stimulation cannot reliably be achieved in oedematous ICU patients and compared with a normal population of anaesthetized patients.

Keywords: monitoring, neuromuscular function; intensive care

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Heart rate variability in patients with severe brain injury

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It has been suggested that measures of heart rate variability (HRV) may be useful in determining outcome in patients with brain injury.[1] [2] However sedation and vasoactive drugs that are frequently required in management may have confounding effects on measures of HRV. The usefulness of HRV measurements in the presence of such confounding factors has not been studied previously in adult patients.

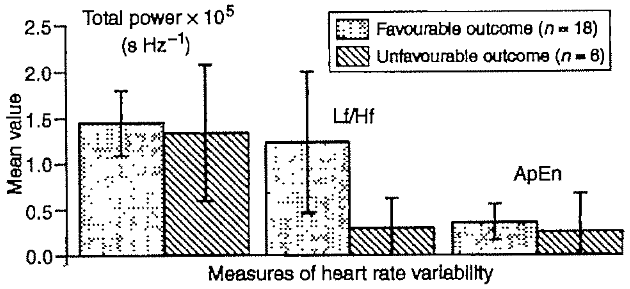

Fig 6 Comparison of HRV measures for favourable and unfavourable outcome.

Twenty-four ventilated patients with brain injury of varying aetiology were studied within 72 h of admission to ICU. Level of sedation was standardized using a modified Ramsay Scoring System. An ECG rhythm strip was recorded for approximately 20 min on a personal computer using a CED 1902 amplifier, CED 1401 AD converter and Spike 2 software (Cambridge Electronics Design, Cambridge) at a sampling rate of 1KHz. Respiratory rate, sedative medication, use of vasoactive drugs and presence of sepsis were noted at the time of recording. The measurements were repeated weekly on patients who remained in the Unit for longer periods. All patients were followed up after discharge and the Glasgow Outcome Score (GOS) on discharge from hospital was recorded. Fast Fourier Transform based on 1024 epochs was used to derive the power spectrum including normalized low frequency (Lf), high frequency (Hf) and total power (Tp).The R wave tachogram was used to calculate approximate entropy (ApEn, N=1000, m=2, r=0.002 s). Clinical outcome was classified as favourable (GOS=3, 4 or 5) or unfavourable (GOS=1 and 2). Multiple regression and Mann–Whitney U tests were used for data analysis and the results are summarized in Figure 6.

Differences between the groups were not statistically significant for any of the parameters studied ($P>0.05$). Though there was a four fold difference in mean Lf/Hf ratio there was considerable overlap in the 95% confidence interval. Multiple regression analysis showed a significant association between the use of noradrenaline (NA) or presence of sepsis and reduction in the Lf/Hf ratio (r^2 =0.45, F=18 and $P<0.01$). This study shows that currently available measures of HRV are nonspecific and do not in isolation predict neurological outcome in the presence of sedation and vasoactive infusions.

Keywords: heart, arrhythmia; head, injury

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Erythrocyte ATP concentration and red cell hypochromasia in criticall illness

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Changes in intracellular electrolyte composition have been demonstrated in erythrocytes of severely ill patients. It is believed

Table 10 Erythrocyte ATP when cell hypochromasia is <10% or ≥10%. $P<0.05$ Mann–Whitney U test

	Erythrocyte ATP (μmol 100 ml^{-1})
Red cell hypochromasia <10%	53.04 (45.6–57.4)
Red cell hypochromasia ≥10%	65.42 (58.9–71.2)

that this is due to an impairment of ATP-dependent Na$^+$/K$^+$ transport and results in an increase in intracellular Na$^+$, a decrease in intracellular K$^+$ and an increase in ATP.[1] The rise in ATP is believed to represent a failure of transport mechanisms rather than an energy deficit within the cell. Red cell hypochromasia has for many years been viewed as synonymous with functional iron deficiency. However, acute development of red cell hypochromasia (>10%) has been shown to be associated with increased duration of intensive care stay and duration of sepsis.[2] Hypochromasia in many critically ill patients is not due to functional iron deficiency but due to an acute increase in red cell volume. The aim of this study was to evaluate the relationship between erythrocyte ATP concentration (and thus susceptibility to osmotic stress) and percentage hypochromasia.

Thirty-one consecutive adult patients admitted to one intensive care unit were studied. Patients were excluded if they had received a recent massive blood transfusion (>8 units), suffered haematological malignancy or chronic renal insufficiency. Percentage red cell hypochromasia was measured on routine blood samples by a Bayer Advia 120 auto-analyser. Red blood cell ATP concentration was determined on deproteinized blood by a spectrophotometric method dependent on the following reactions:

ATP+3-Phosphoglycerate→ADP+1,3 Diphosphoglycerate

1,3 Diphosphoglycerate+NADH→Glyceraldehyde-3-P+NAD+P

The decrease in measured absorption due to the oxidation of NADH is proportional to ATP erythrocyte content.

Six patients (19%) had hypochromasia greater then 10%. Results are expressed (Table 10) as median (inter-quartile range).

Red cell hypochromasia is associated with a significant increase in intracellular ATP concentration. This may represent a failure of the normal homeostatic mechanism of the erythrocyte and a decrease in Na$^+$/K$^+$ ATPase activity. The failure of this enzyme to regulate the normal transmembrane electrolyte gradient may result in an increase in mean cell volume. This would be consistent with the finding of red cell hypochromasia independent of functional iron deficiency in critically ill patients.[3] A further study is needed to confirm this finding in a larger population and its effect on erythrocyte function.

Keywords: blood, erythrocytes; intensive care

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Effects of transient changes in tidal volume on carbon dioxide evolution in intensive care patients

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Because the body stores of carbon dioxide are large, steady state is achieved slowly when a change in ventilator setting changes carbon dioxide removal rate. Adjusting ventilation for satisfactory gas exchange can thus be lengthy, if a steady state of gas exchange is sought after each adjustment. We thought that if transient changes are imposed, breath by breath carbon dioxide output could indicate the effect of this change, and allow rapid estimation of the likely effects of ventilator adjustment.

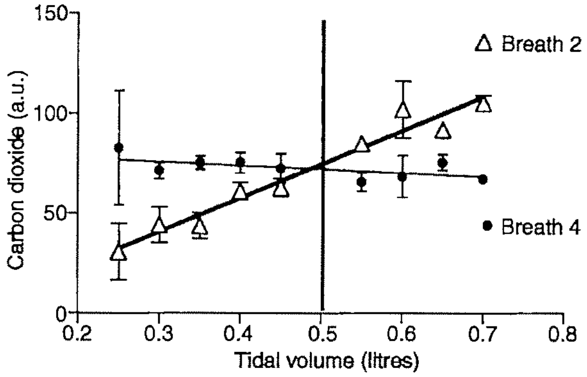

Fig 7 Carbon dioxide output during and after the imposed change in tidal volume.

We studied three patients in the intensive care unit receiving volume preset mechanical ventilation for acute lung injury. Digital data for exhaled flow and carbon dioxide concentration were obtained from a Dräger Evita 4 ventilator, fitted with an in-line cuvette for carbon dioxide analysis. We used the software package Labview, to multiply exhaled flow and carbon dioxide values, and integrated to calculate carbon dioxide production per breath. These values along with other information from the ventilator were recorded using custom written software and further analysed by the software package Prism version 3. We changed the tidal volume setting on the ventilator to give a two-breath change, and recorded the carbon dioxide output in the breaths before (breath zero), during (breaths 1 and 2), and for three breaths (3 to 5) after the change in tidal volume. Tidal volumes were increased and decreased from 200 to 750 ml. Each tidal volume was applied three times. Each patient was studied with a full set of tidal volume changes in this way between 4 and 8 times. The relationship between mean exhaled carbon dioxide and tidal volume was tested by linear regression.

Carbon dioxide output for breaths 1 and 2 changed in proportion to the applied tidal volume (Figure 7). The output for breath 4 was not significantly different from the control breath output, showing that there was no carry-over of the tidal volume change.

Keywords: intensive care; ventilation

Acknowledgement

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The role of nitric oxide synthase in the development and expression of tolerance to the alpha$_2$ agonist dexmedetomidine

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Alpha$_2$ agonists are now being advocated for prolonged periods of administration because of their potential benefit at each stage in the surgical patient's care, especially for sedation, analgesia and cardiovascular stability. However, biologically important adaptations to the immediate effects of alpha$_2$ agonists may lead to diminished drug effects over time; this is generally termed tolerance. Tolerance may mitigate the clinical utility of alpha$_2$ agonists for chronic pain relief and prolonged sedation in the intensive care unit (ICU) setting. We have investigated the role of nitric oxide synthase (NOS) for the induction and maintenance of tolerance to the sedative actions of dexmedetomidine (DEX), a highly-selective and potent alpha$_2$ agonist in rodent models. Pharmacological data in rats[1] indicate that NOS is involved although it is not clear whether nitric oxide (NO) is sufficient to initiate the tolerance cascade. NOS is not involved in the development of tolerance to the analgesic actions of dexmedetomidine[1]. To further define the role of NOS in alpha$_2$ tolerance, and whether it is the inducible (iNOS) or neuronal (nNOS) variety studies need to be conducted in mice in which selective deficiencies of these two species of NOS can be developed through null mutations ('knockouts'). This has required the development of a mouse model of alpha$_2$ tolerance.

Changes in the sedative and analgesic effects of dexmedetomidine after prolonged administration of DEX to 129/BL6 mice were examined. This is the background strain for the NOS knockout mice. Acute administration of DEX caused a dose dependent increase in sedation as monitored by open field activity with a maximum effect at $10\ \mu g\ kg^{-1}$ and in analgesia using the Hargreaves test with a maximum effect at $100\ \mu g\ kg^{-1}$. These effects were blocked by administration of the alpha$_2$ antagonist RX821002 ($2\ mg\ kg^{-1}$). Robust tolerance to the analgesic and sedative effects of dexmedetomidine ($50\ \mu g\ kg^{-1}$) were observed with 5 days of dexmedetomidine exposure.

Now that we have established a mouse model in which tolerance develops to the behavioural actions of an alpha$_2$ agonist, we can explore the definitive roles of the inducible and neuronal forms of NOS using genetically altered animals with deficiencies in iNOS or nNOS.

Keywords: model, mouse; analgesics, dexmedetomidine; enzymes, nitric oxide synthase

Acknowledgements

This work was supported by the Medical Research Council, the United States National Institutes of Health and the Department of Veterans Affairs. Y.K.A. is a SIMS Portex Fellow.

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First clinical experiences with a new depth-of-anaesthesia monitor

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Respiratory sinus arrhythmia (RSA) varies with depth of anaesthesia.[1] The Fathom monitor (Amtec Medical, Antrim) is the first commercially-developed device based on this principle, and uses circular RSA analysis.[2] In this preliminary clinical investigation we aimed to establish, in broad terms, whether Fathom reflects anaesthetic depth as judged on clinical grounds.

We studied nine unpremedicated adult patients (4 male, 5 female, median age 59 yr) undergoing general anaesthesia without neuromuscular blockade. In addition to standard patient monitoring, four extra ECG electrodes were attached and a Magtrak turbine (Ferraris Medical Ltd) was inserted at the patient end of the breathing system. A baseline reading for RSA was obtained during face-mask preoxygenation. RSA was then monitored continuously throughout anaesthesia by one of the investigators, who did not take part in the conduct of the anaesthetic. Readings were documented at six further points during the procedure. Patient movement, if any, and other clinical responses to stimuli were noted. The monitor screen was hidden from the anaesthetist caring for the patient.

Table 11 RSA as percentage of machine reference value, median (range)

	Percentage
Baseline (awake)	89 (22–99)
Before LMA insertion	41 (8–87)
After LMA insertion	37 (14–95)
Before surgical incision	29 (15–59)
After surgical incision	41 (17–85)
Two minutes before awakening	48 (24–122)
On awakening	25 (8–81)

Fathom's software displays an RSA number on screen, a reference value having been established in awake young adults. It also displays each patient's RSA reading as a percentage of this reference value, and this is how our results are presented (Table 11).

Our real-time observations suggest that Fathom parallels clinical expectations of anaesthetic depth. We cannot however explain why RSA values, having risen after anaesthesia is discontinued, fall again before clinical awakening. There is also considerable variation in baseline values, which cannot be attributed entirely to the lower vagal tone of our patients compared with the monitor's younger reference subjects. Finally, low patient tidal volumes were associated with less reliable readings, but we feel this may be improved by using a more sensitive flow sensor.

Keywords: heart, arrhythmia, respiratory sinus; anaesthesia, depth

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Bacterial challenge testing of epidural filters

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Epidural infection is a serious although rare complication of epidural catheterization. Of the three possible routes of microorganism entry (haematogenous, skin insertion site, catheter hub), the epidural catheter hub appears to represent the main route of catheter microbial colonization.[1] Since the use of bacterial filters in clinical practice represent a valuable tool for preventing epidural colonization it is important to estimate their antimicrobial efficacy especially during extended use. The aim of this study was to assess the antimicrobial characteristics of a recently developed epidural filter over 120 h using bacterial challenge testing.

Ten SIMS Portex epidural filters ($0.2\ \mu m$, polysulphone membrane filter), previously sterilized with ethylene oxide, were subjected to bacterial challenge testing using the bacteria Brevundimonas diminutia (BD). Following a preliminary assessment of the survival of BD over 24 h in sterile water, each epidural filter was connected via sterile tubing to a 1 litre bottle of distilled sterile water containing a BD challenge suspension of approximately 1×10^4 cfu ml^{-1} (colony forming units per ml). The gravity fed filtrate was collected downstream of the epidural filter into a pre-weighed sterile 1 litre glass collection bottle with a 26G, 1 cm needle regulating flow to 10–50 ml h^{-1}. The concentration of BD in the challenge suspension was assayed at 0, 7 and 24 h. After each 24 h period, the filtrate in the collection bottle was weighed and any BD breakthrough assayed by filtering the entire contents through a 0.2 µm Cyclopore 47 mm membrane filter. Each Cyclopore filter was placed on a Tryptone Soya Broth Agar (TSBA) plate which was then incubated at 30°C for 72 h. A fresh 1 litre of BD culture suspension and a sterile collection bottle were replaced every 24 h. Microbial growth was assessed as colony forming units per ml of solution. The filtration procedure was carried out over 120 h for each of the 10 epidural filters together with positive (0.8 µm membrane filter) and negative (BD free challenge solution) laboratory controls. Statistical analysis included Kolmogorov-Smirnov normality testing, as well as unpaired *t* test and repeated measures ANOVA for the summary data ($P<0.05$).

BD challenge levels for the epidural filters were maintained over 1×10^3 cfu ml^{-1} throughout the 120 h test period with an overall mean (SD) count of 1.10×10^4 (0.23×10^4) cfu ml^{-1}. The mean (SD) volume of filtrate over each 24 h period was 593.28 (170.13) ml. BD was not detected in any filtrate collected downstream of the 10 epidural filters tested. Although the positive control, with a larger 0.8 µm filter pore size compared to the epidural filters, gave a total breakthrough of 1×10^4 cfu ml^{-1} of BD at 24 h, this declined to 0 cfu ml^{-1} over the remaining 120 h test period. There was no microbial growth in the negative controls over the test period. These experiments show that the 0.2 µm polysulphone membrane epidural filters tested prevented the passage of a high challenge of the microorganism BD over a 120 h period. The 0.8 µm filter proved inadequate as a positive control due to possible microbial cell blockage.

Keywords: complications, infections, epidural

Acknowledgements

SIMS Portex Ltd for study funding and Research Fellowship (JRD).

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Effects of volume replacement on plasma volume and albumin escape rate in a porcine model of septic shock

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Capillary leakage syndrome is characterized by loss of intravasal fluids leading to generalized oedema and haemodynamic instability despite massive fluid therapy. Use of hydroxyethyl starch (HES) molecules has been suggested to 'plug' the capillary leaks.[1 2]

In a prospective randomized, controlled animal laboratory study, fasted, anaesthetized, mechanically ventilated and multi catheterized pigs (20.8 (1.8) kg) received 1 g kg^{-1} body weight faeces into the abdominal cavity to induce sepsis and were observed over 8 h. At induction, animals were randomized to resuscitation with modified fluid gelatin 8% (MFG8%) (n=5), modified fluid gelatin 4% (MFG4%) (n=5), 6% HES 200/0.5 (n=5), Ringer's solution (RS) (n=5) and compared to a non-septic group (n=5) receiving 6% HES 200/0.5. Infusion rate was titrated to maintain a central venous pressure of 12 mm Hg. Blood volume was analysed using chromium-51-tagged erythrocytes. PV was determined from standard formulae. Albumin escape rate (AER) was calculated using technetium 99m-labelled human serum albumin. Colloid osmotic pressure (COP), systemic haemodynamics and oxygenation were obtained before, 4 and 8 h after induction of sepsis. Data are presented as mean (SD). Statistical intergroup comparison was performed using Wilks-Lambda and Ryan-Einot-Gabriel-Welsh-F-test.

Plasma volume was reduced in Ringer's solution-group, but could be maintained or even increased by colloids indicating better intravascular persistency (Table 12). Albumin escape rate was increased in all colloid groups and Ringer's solution-group compared to non-septic group with no differences between groups. Colloid osmotic pressure was increased by colloids and decreased in Ringer's solution-group. Thus, we suggest that maintenance of intravascular volume in septic shock by colloids is due to an osmotic effect rather than the proposed direct occlusive effect on injured capillary endothelium.

Keywords: blood, volume replacement; blood, sepsis

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Table 12 Fluid compartments, AER and COP; intergroup comparison. *$P<0.05$ was considered significant

	Sepsis **RS**	**Sepsis** **MFG 8%**	**Sepsis** **MFG 4%**	**Sepsis** **HES**	**No Sepsis** **HES**
RBC (ml kg^{-1})					
Preshock	23.2 (2.6)	20.1 (1.9)	21.1 (2.6)	22.1 (2.5)	24.7 (1.6)
8 h	18.9 (1.4)	20.2 (1.7)	19.8 (2.8)	21.2 (2.0)	25.6 (1.5)*
PV (ml kg^{-1})					
Preshock	61.0 (2.2)	60.0 (5.1)	57.3 (5.9	59.0 (8.1)	65.5 (7.7)
8 h	32.9 (2.9)*	73.9 (7.9)*	54.8 (9.5)	59.1 (11.1)	79.8 (6.8)*
AER (%)					
4 h	21 (2)	24 (9)	24 (3)	22 (4)	3 (3)*
8 h	8 (2)	11 (8)	10 (3)	8 (3)	–2 (4)*
COP (mm Hg)					
Preshock	11 (2)	10 (1)	11 (1)	11 (1)	10 (0)
8h	5 (1)	16 (3)	13 (3)	15 (4)	17 (2)

Reduction in postoperative supraventricular dysrhythmias following CABG by nicorandil

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Supraventricular dysrhythmias (SVT) following coronary artery bypass surgery (CABG) occur in up to 50% of cases and have been associated with increases in duration of stay and hospital costs. The overwhelming majority of SVTs are due to atrial fibrillation (AF). Ventricular dysrhythmias are substantially less common but are a life-threatening complication of CABG.

The electrophysiologic mechanism underling postoperative AF is believed to be that reentry results from dispersion of atrial refractoriness.[1] Myocardial ischaemia shortens the action potential duration, an effect reduced by ischaemic preconditioning and the K_{ATP} channel opener pindacidil.[2] Pinacidil reduces ventricular dysrhythmias after myocardial ischaemia in rabbits.[2] Nicorandil is a hybrid K_{ATP} opener and nitrate that is used increasingly in the management of patients with ischaemic heart disease. We hypothesized that nicorandil might reduce the incidence of dysrhythmias after CABG.

We studied records from 3860 patients undergoing isolated CABG over a 42 month period. 641 patients underwent CABG without cardiopulmonary bypass (CPB) as described by Angelini.[3] The remainder underwent CABG using conventional CPB with myocardial preservation according to the Calafiore technique.[4 5]

The incidence of dysrhythmias and requirements for pacing is shown in Table 13.

This is the first time that a K_{ATP} channel opener has been associated with a reduction in the incidence of SVT following CABG in man. The relatively low incidence of SVT in the control group of patients operated on with CPB probably reflect the use of magnesium in the cardioplegia[6]. It is interesting that those patients operated on without CPB and not subjected to complete ischaemia, albeit with cardioplegic protection, have a substantially lower incidence of dysrhythmias, nicorandil is of no benefit in this group at preventing dysrhythmias.

Keywords: surgery, coronary artery bypass; complications, arrhythmia; ions, ion channels, nicorandil

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Table 13 Reductions in dysrhythmias by nicorandil following CABG *$P<0.005$ *vs* control

	CABG with CPB		**CABG without CPB**	
Post op	**Control incidence (%)**	**Nicorandil Relative +Risk (95% CI)**	**Control incidence (%)**	**Nicorandil Relative Risk (95% CI)**
SVT	15.4	0.574 (0.396–0.834)*	9.5	0.868 (0.426–1.77)
VT/VF	2.3	0.499 (0.181–1.38)	0.97	0.861 (0.100–7.43)
Temp Pacing	4.61	1.53 (0.967–2.42)	1.74	1.95 (0.589–6.43)
Perm Pacing	0.93	1.37 (0.574–3.28)	0.77	1.08 (0.119–9.73)

Cerebral oxygenation during warm (35 (1)°C) and cold (25 (1)°C) cardiopulmonary bypass in children undergoing open-heart surgery

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Near-infrared spectroscopy is a potentially useful non-invasive monitoring method for cerebral oxygenation and metabolism in infants and children undergoing cardiac surgery.[1] There is a potential risk of impaired cerebral oxygenation during warm cardiopulmonary bypass (CPB) due to lack of hypothermic brain protection. To our knowledge, no studies have been performed to compare cerebral oxygenation during warm and cold CPB surgery in children. The aim of this preliminary study was to compare the changes of cerebral oxygenation during cold and warm bypass surgery in children undergoing open-heart surgery.

Eighteen patients were equally assigned by minimization[2] to balanced groups, either to warm or cold CPB. Cerebral oxygenation was monitored continuously from the onset of surgery till after CPB and was averaged at the following time periods; before CPB, after 5, 20, 40 min on CPB and at the start of rewarming and end of rewarming, 5 min before end of CPB and 10 min after CPB. NIRO-300 was used to monitor oxygenated (HbO_2) and deoxygenated haemoglobin (HHb), oxidized cytochrome aa3 (CytOx), and tissue oxygen index (TOI) by spatially-resolved spectroscopy (SRS). TOI represents the averaged regional cerebral haemoglobin saturation. Mean CPB values of NIRS parameters and lowest values of HbO_2, TOI and CytOx, and highest values of HHb were used for statistical analysis.[3] Mann–Whitney U test and independent-samples *t* test were used as appropriate.

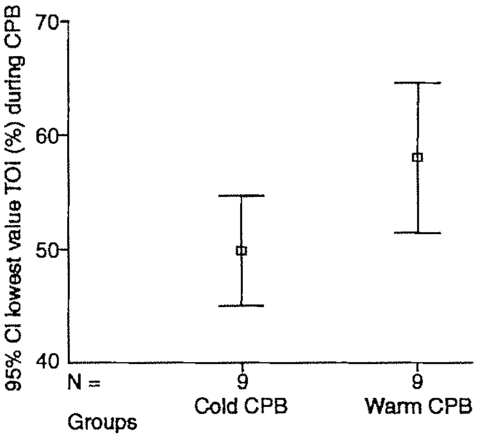

Fig 8 Mean and 95% CI of lowest values of TOI during warm and cold CPB.

During CPB, there was no difference in HbO_2, HHb and CytOx values between the two groups. The mean lowest value of TOI was significantly (P=0.035) lower during cold CPB (Figure 8). Five patients were desaturated (TOI of ≤50%) mainly during rewarming in the cold group, and only two patients had TOI of 50% during warm bypass.

This preliminary study suggests that cerebral oxygenation may be preserved in children undergoing warm CPB.

Keywords: surgery, cardiopulmonary bypass; children

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The effects of halothane on action potential configuration of sub-epicardial and sub-endocardial cells from normal and hypertrophied rat left ventricle

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Halothane inhibits the transient outward K^+ current (I_{to}).[1] As I_{to} is greater in ventricular sub-epicardium (EPI) than in sub-endocardium (ENDO), halothane may have differential effects on action potential (AP) configuration in EPI and ENDO cells. In addition, ventricular hypertrophy is associated with a prolongation of the AP reflecting changes in the expression of ion channels, which may also influence halothane-induced effects on AP configuration.

Individual EPI and ENDO cells were isolated from the left ventricle of 20 week old male spontaneously hypertensive rats (SHR) and normotensive control Wistar-Kyoto rats (WKY) using a standard enzymatic dissociation protocol. AP recordings were made at 30°C in current-clamp mode using the perforated patch technique before, during and after a 1 min exposure to 0.6 mM halothane (Fig. 9A). Data are given as mean (SEM). Statistical analysis was carried out using paired or unpaired Student's t-tests as appropriate. Under control conditions, in both WKY and SHR, AP duration (APD), measured as time (ms) to repolarise to –50 mV, was shorter in EPI cells than ENDO cells (WKY EPI, 21 (2), n=10; ENDO, 37 (5), n=13; SHR EPI, 34 (7), n=6; ENDO, 73 (13), n=7, Fig. 9B). ENDO APD was significantly greater in SHR than WKY cells (P=0.007). Halothane induced a reversible sustained reduction of APD (ms) in all cell types (WKY EPI, 19 (2), P=0.003; ENDO 28 (3), P<0.001; SHR EPI 25 (4), P=0.045; ENDO 35 (4), P=0.004). Figure 9B shows that halothane decreased the difference between EPI APD and ENDO APD, and that this effect was more pronounced in SHR. This reduction in the transmural dispersion of refractoriness could contribute to the arrhythmogenic properties of halothane observed in the clinical situation, an effect which appears more marked in the hypertrophied heart.

Keywords: heart, ventricular hypertrophy, action potential; anaesthetics volatile, halothane

Acknowledgement

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Effects of halothane on contraction of sub-endocardial and sub-epicardial rat cells from normal and hypertrophied left ventricle

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Halothane inhibits several cardiac ionic currents e.g. I_{Na}, I_{Ca} and I_{to}. I_{to}, which contributes to the initial repolarization phase of the action potential, is greater in the sub-epicardium (EPI) than the sub-endocardium (ENDO). As a result, halothane may have differential transmural effects on action potential configuration and contraction. In addition, ventricular hypertrophy is associated with changes in the expression of sarcolemmal ion channels and calcium handling proteins, changes which may also modify the inotropic response to halothane.

ENDO and EPI cells were isolated from 20 week old male normotensive Wistar-Kyoto (WKY) and spontaneously hyperten-

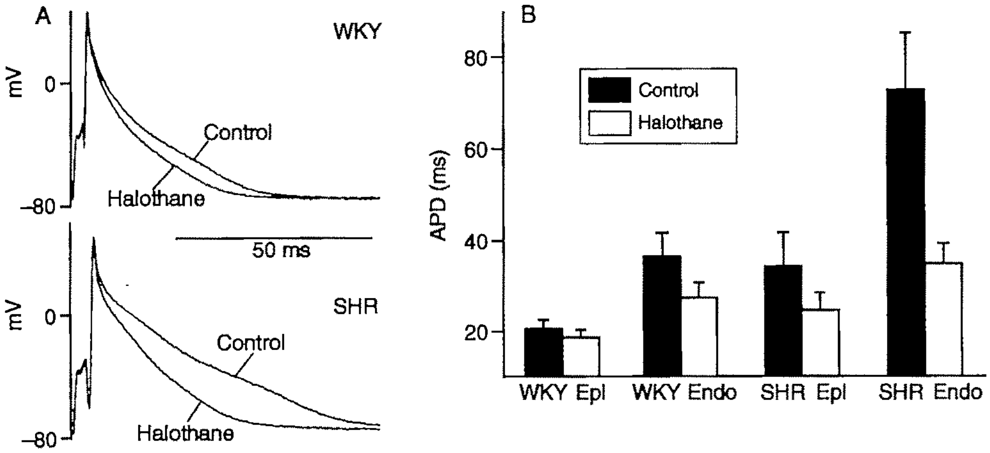

Fig 9 (A) representative action potential recordings from WKY and SHR ENDO cells before and during exposure to halothane. (B) mean data (±SEM) showing the sustained effect of halothane on APD in SHR and WKY EPI and ENDO cells.

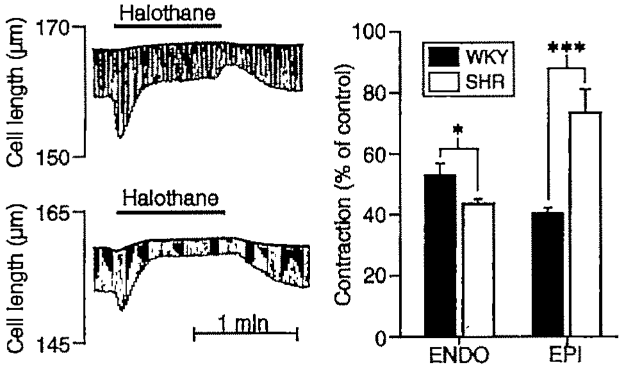

Fig 10 (A) cell length records from SHR EPI (top) and WKY EPI cells (lower) during a 1 min exposure to halothane. (B) mean data (±SEM) describing the sustained negative inotropic effects of halothane in SHR and WKY cells (*$P<0.05$, ***$P<0.001$).

sive rats (SHR) using a standard enzymatic dissociation protocol. Cell contraction, induced by field stimulation (100 V, 2 ms duration, 1 Hz), was recorded optically before, during and after a 1 min exposure to 0.6 mM halothane ($\sim 2\times MAC_{50}$) at 37°C in the four cell types. Data are expressed as mean percentage of control (SEM) with Student *t*-tests providing the level of significance.

In SHR, regional hypertrophy was detected: cross sectional area of SHR ENDO cells was 168 (15)% of WKY ENDO cells ($P=0.002$) but in SHR EPI cells was only 112 (8)% of WKY EPI cells. Figure 10A shows representative cell length records of SHR and WKY EPI cells during an exposure to halothane. At the end of an exposure, contraction was reduced to a greater extent ($P=0.008$) in SHR ENDO (to 44 (2)%, $n=6$) than EPI cells (to 73 (8)%, $n=9$). Conversely, in WKY cells, contraction was reduced to a greater extent ($P=0.008$) in EPI (to 41 (2)%, $n=8$) than ENDO cells (to 53 (4)%, $n=8$). In SHR cells, there was a further transient reduction in contraction on wash-off of halothane (ENDO, to 24 (8)%; EPI, to 60 (5)%; both $P=0.03$, see Fig. 10A) which was not observed in WKY cells. These data show that a clinically relevant dose of halothane induces differential transmural effects on contraction: in WKY cells, contraction is reduced to a greater extent in EPI *vs* ENDO but in hypertrophied cells the reverse is seen (Figure 10B).

Keywords: heart, ventricular hypertrophy, contraction; anaesthetics volatile, halothane

Acknowledgement

This work was supported by the British Journal of Anaesthesia and British Heart Foundation.

Rapid sequence intubation without the use of neuromuscular blockade? A double blind randomized controlled trial

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Several studies have shown that it is possible to perform tracheal intubation without the use of muscle relaxants during elective surgery.[1–5] It is common to perform rapid sequence induction (RSI) for emergency surgery when intubation follows the administration of thiopentone and succinylcholine. Little information exists on rapid sequence intubation using induction agents without succinylcholine. We investigated this to see if it would be possible.

Patients (ASA I or II) undergoing emergency appendicectomy were allocated randomly into two groups. Group t/s ($n=20$) received a standard RSI with thiopentone 6 mg kg^{-1} and succinylcholine 100 mg. While group m/p/r ($n=20$) received midazolam 0.06 mg kg^{-1} 3 min prior to induction followed by propofol 1.25 mg kg^{-1} and remifentanil 2 µg kg^{-1} as a bolus. All patients were intubated 60 s after the final drug delivery by an anaesthetist who was blinded to the patient's grouping. Intubating conditions were assessed by jaw relaxation, ease of laryngoscopy, coughing, vocal cord and limb movement. Each category was scored on a scale 1–4 (1=excellent and 4=very poor) giving a minimum score of 5 and a maximum of 20. Heart rate (HR), blood pressure (BP) and oxygen saturation were recorded preinduction, 2.5 min postmidazolam and 60 s after intubation. Postoperative follow up the next day assessed myalgia, sore throat and patient satisfaction.

There was no significant difference in gender, age and weight between groups. Mean (SD) intubation scores were significantly different (t/s group 5.7 (1.2) *vs* m/p/r group 7.6 (2.4) $P<0.01$). Excellent intubation scores (=5) were achieved in 13 *vs* 4 patients in the t/s or m/p/r group respectively. Two patients in the m/p/r group had very difficult laryngoscopies and one of these required a further dose of propofol (1.25 mg kg^{-1}) to facilitate intubation but all patients were successfully intubated. There was also a significant difference in the cardiovascular response to tracheal intubation (60 s postintubation-systolic BP 162 (23) *vs* 118 (21) $P<0.01$ and HR 107 (17) *vs* 79 (19) $P<0.01$ for t/s, m/p/r group respectively. On follow up, four patients in the t/s group complained of myalgia and three patients had recall of cricoid pressure application.

Despite rapid sequence intubation being possible using midazolam, remifentanil and propofol, the study demonstrates a significantly worse intubation score compared to treatment with thiopentone and succinylcholine. Further refinement of the drug dosages and timing may be necessary to achieve optimal conditions before recommending this technique be used for rapid sequence intubation.

Keywords: anaesthetic techniques, induction

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Holter (ECG) monitoring of senior medical staff at work

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There is little preventative health monitoring for senior clinical staff in most NHS hospitals, apart from hepatitis B status, despite the huge cost of extended sick leave when major illness strikes. Some commercial organizations undertake regular health checks on their senior staff, the British army performs 5-yearly medical examinations (but not ECG) on all military personnel over 40 and airline pilots require an annual health check with ECG. We

Table 14 Heart rate and frequency of abnormal rhythm (abnormal in **bold**)

	Durn of record hours.min	Heart rate			Ventricular ectopics	Supravent ectopics	Other abnorm
		Min	Mean	Max			
Anaes1	14.09	56	83	126	4	2	–
Anaes2	13:14	65	**98**	**153**	**258**	1	–
Anaes3	9.32	48	65	106	14	7	–
Anaes4	17.16	52	70	138	0	3	–
Surg 1	8.49	63	84	121	1	8	–
Surg 2	18.12	52	87	142	6	4	**LBBB**
Surg 3	12.08	61	84	111	1	1	–
Surg 4	13.14	58	74	106	0	41	–
Surg 5	16.20	57	74	109	29	73	–
Surg 6	15.37	63	92	125	3	11	–

monitored ambulatory ECGs during the normal working day of anaesthetic and surgical consultants aged over 50 yr. None were on any cardiovascular medication or had any (known) history of cardiovascular disease.

The monitor (Marquette Seer M.C.) recorded ambulatory ECG from 5 electrodes (LL, LA, RL, RA, C). Recordings started before leaving home for work and usually finished that evening, once back at home. A simple diary of the day's activity was kept. ECG data, recorded digitally onto flash cards was downloaded onto a Marquette Mars 8000 analyser.

Ten subjects were recorded; four consultant anaesthetists and six consultant surgeons, all aged between 50 and 57 (Table 14). Two recordings out of the 10 gave cause for concern. One surgeon was found to have a serious conduction defect needing urgent investigation. One anaesthetist showed a high incidence of ectopics and a high heart rate. These were not however related to clinical episodes in theatre and the highest heart rate occurred during a committee meeting! The remaining eight recordings were remarkable for the low frequency of abnormal events, despite far from uneventful diary entries.

We conclude that many senior clinicians are remarkably cardiovascularly healthy but there may be some with developing disease who could benefit from early therapy before serious disability and sickness develops. There may be a clear cost and health benefit to give all senior staff regular health screening, including ambulatory ECG (as well as BP, urinalysis, and weight). Who should pay for this?

Keywords: monitoring, electrocardiography; medical personnel

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Preston and Chorley Research fund for the Holter monitor.

Intra-operative fluid optimization using the oesophageal Doppler during bowel surgery: effect on cardiac output

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Oesophageal Doppler Monitoring (ODM) allows non-invasive continuous measurement of corrected flow time (FTc), stroke volume (SV) and cardiac output (CO).[1] Intravascular volume optimization using ODM during femoral fracture repair has been shown to improve cardiac output and reduce length of hospital stay.[2] We studied the impact of fluid titration with ODM during major bowel surgery.

Table 15 Haemodynamic variables measured by ODM at the beginning and end of surgery. Values are mean (SD). *Final intervention *vs* control, $P<0.05$

		Control	Intervention
	n	28	26
Flow time (corrected) s	Initial	0.352 (0.038)	0.338 (0.023)
	Final	0.351 (0.046)	0.380 (0.031)*
Stroke volume ml	Initial	71.5 (19.9)	69.6 (16.6)
	Final	67.7 (18.9)	81 (23.4)*
Cardiac output litres min^{-1}	Initial	4.6 (1.3)	4.3 (1.4)
	Final	4.9 (1.4)	5.8 (1.7)*

Fifty-six patients undergoing major bowel surgery participated in the study. During a standardized anaesthetic the ODM probe (Medicina UK) was placed at mid-oesophagus by the investigator. Patients were assigned randomly to intervention (I) or control (C) groups. All patients received intra-operative fluid therapy at the discretion of the non investigating anaesthetist in accordance with their normal practice. In addition, Group I received hydroxyethyl starch boluses (3 ml kg^{-1}) using a protocol guided by ODM measurements of FTc and SV. Cardiac output was calculated by the ODM. Linear regression for group effects and *t*-test were used to compare data.

The groups were similar for age, weight, height, gender, ASA grade, Goldman Score and pre-operative haemoglobin. All patients had pre-operative bowel prep. Of 56 patients recruited (I:C 28:28), two from Group I were withdrawn due to problems with the probe. Group I received significantly more intra-operative colloid than Group C: 28 (16) *vs* 19.4 (14.7) ml kg^{-1} mean (SD), $P=0.02$. SV, FTc and CO increased significantly in the intervention group whilst controls remained unchanged (Table 15). The mean difference (95% CI) in final cardiac output was 0.87 litres min^{-1} (0.31,1.43) $P=0.003$. No difference was detected in hospital stay: median 11 days.

Intra-operative fluid titration using the oesophageal doppler monitor can lead to improved haemodynamic parameters during major elective surgery. More patients need to be studied to determine whether this leads to a reduction in hospital stay.

Keywords: heart, cardiac output; measurement techniques, Doppler ultrasound; surgery, gastrointestinal

Acknowledgement

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Clinical rather than biochemical variability may predict mortality following oesophagectomies

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We have previously reported the 'normal' course of microalbuminuria (MA) and serum procalcitonin (PCT) levels following elective oesophagectomy.[1 2] The aim of this study was to evaluate the predictive value of biochemical markers such as: PCT, C-reactive protein (CRP) and MA; compared to clinical parameters.

Patients following oesophagectomy were studied for the first 3 postoperative days. Serum PCT, CRP and MA levels were determined daily. The patients' clinical course and organ dysfunction was monitored by the Multiple Organ Dysfunction Scoring System (MODS).[3] For statistical analysis Mann–Whitney and multiple logistic regression were used as appropriate.

Of the 65 patients studied survivors (S, n=56) were compared to non-survivors (NS, n=9). The course of MA, PCT and CRP levels showed a similar pattern as described previously, with no significant difference between S and NS, however MODS were significantly higher in the NS group on each day. Regarding organ dysfunction only the respiratory dysfunction score (Pa_{O_2}/FI_{O_2}: mm Hg) showed significant differences between the two groups; 172 (71) *vs* 299 (154) P=0.001; 155 (84) *vs* 263 (98) P=0.004; 134 (81) *vs* 250 (91) p=0.002; (NS *vs* S; postoperative days 1, 2 and 3 respectively). There was also a significant correlation with mortality (P=0.02).

This study found, that the investigated biochemical markers could not differentiate between the S and NS groups in the early postoperative period following oesophagectomy. Respiratory function was the only investigated parameter that showed significant correlation with outcome.

Keywords: surgery, oesophagectomy; complications, mortality

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A randomized, open, parallel group study to compare recovery with a remifentanil or fentanyl based anaesthetic for adult patients undergoing elective cardiac surgery

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There has been growing interest in the fast-tracking of cardiac surgical patients to facilitate more surgery.[1] While high dose opioids such as fentanyl have been the mainstay of anaesthesia for patients undergoing cardiac surgery, the newer opioid remifentanil has advantages of non-organ dependent elimination and a short context sensitive half time with possibility of early recovery.[2] The aim of this study was to assess the recovery and discharge times using a fentanyl or remifentanil based anaesthetic in unselected adult patients undergoing cardiac surgery.

Two hundred adult patients were included in this study. They were allocated randomly to a remifentanil-propofol or a fentanyl-propofol anaesthetic in a ratio of 2:1. Following premedication with morphine and lorazepam, anaesthesia was induced with propofol to a target concentration of 1.5 µg ml^{-1} and remifentanil 1.0 µg kg^{-1} followed by an infusion, or fentanyl 5–10 µg kg^{-1} followed by further doses as required. Pancuronium was used for muscle relaxation and anaesthesia was adjusted according to clinical needs. Standard haemodynamic monitoring was used in all patients. Patients in the remifentanil group received morphine 20 mg after rewarming. Sedation in the Intensive care unit (ICU) was with propofol 1–3 mg kg^{-1} h^{-1} and remifentanil and morphine respectively. Standard criteria were used to establish readiness for extubation, discharge from the ICU, the high dependency unit (HDU) and the hospital. The haemodynamic responses, the drug dosages and the times for extubation and discharges were recorded. Comparisons between the groups were obtained using the independent sample t-tests and the Mann–Whitney U test.

There were no significant differences in demographic data, duration of aortic cross-clamping or surgery times. The amount of propofol given was 12.5 and 16.5 mg kg^{-1} respectively in the remifentanil and fentanyl groups (P<0.05). Patients in the remifentanil group had lower HR and SAP at skin incision and sternotomy (P<0.005). Extubation in the ICU was achieved significantly earlier in the remifentanil group (Table 16; P<0.05) but the times to discharge from the ICU, HDU or the hospital were not significantly different. The odds of extubating patients on the day of surgery were 2.94 times greater in the remifentanil group.

In conclusion, the use of remifentanil allowed the use of lower doses of propofol and facilitated early extubation. There was however, no difference in discharge times from the ICU, HDU or the hospital.

Keywords: anaesthesia, recovery; analgesics opioids, remifentanil; analgesics opioids, fentanyl

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Table 16 Extubation and discharge times (h; median and inter-quartile range); *P<0.05

		Discharge times		
Group	**Extubation**	**From the ICU**	**From the HDU**	**From the ward**
Remifentanil	11.1 (5.0–19.3)*	22.5 (19.8–23.9)	46.4 (44.3–49.9)	166.3 (142.4–183.5)
Fentanyl	18.1 (7.3–19.7)*	22.4 (20.3–26.0)	47.1 (45.2–50.3)	168.8 (145.9–193.0)

Nerve stimulator current and regional nerve block efficacy

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A nerve stimulator and insulated needle may assist identification of peripheral nerves. Clinically, failure to elicit patella and foot movement is often associated with inadequate analgesia with femoral and sciatic blocks respectively. Instructions for the Stimuplex-Dig (B. Braun, Melsungen) advise moving the stimulating needle until muscle contractions are still visible when current is reduced to 0.2 mA.[1] Clinical studies accept higher currents.[2 3] We have compared the minimum stimulating current eliciting contractions during regional blocks with pain scores and patient controlled analgesia (PCA) morphine consumption i.v.

Patients were anaesthetized for knee arthroplasty. Femoral 3-in-1 and sciatic nerves were blocked using plain 0.375% bupivacaine 20 ml each nerve, through 50 and 150 mm short bevelled Stimuplex insulated needles. Nerves were initially identified with currents of 5 mA. Stimulating currents were then decreased to the lowest current which elicited visible movement. This current was recorded. Patients received alfentanil i.v. intraoperatively and enteral paracetamol and diclofenac after surgery. Patients also had access to PCA morphine 1 mg i.v. with a lockout of 5 min for at least 24 h. All procedures were performed in the presence of SJG. Pain scores on a 4 point scale were recorded by recovery staff (0-no pain, 1-mild, 2-moderate, 3-severe). Patients gave an assessment of pain in the 24 h after surgery using the same scale. Patients and recovery staff were blind to minimum stimulating current. Morphine PCA consumption was recorded two hourly.

Forty-eight patients were studied: 23 were male. Patients were aged 67 (29–89) yr, with weight 75 (13) kg and height 169 (9) cm (mean (SD)). Minimum current for the femoral nerve was 0.6 (0.7) mA, sciatic nerve 0.8 (0.9) mA, and both nerves 1.0 (1.5) mA. PCA morphine delivered was 26 (17) mg. Pain scores in the recovery room were 0.5 (0–2) at rest, and 1 (0–3) on movement (median (IQ range)). Patients' perception of pain over 24 h after surgery was 1 (0.75–2). A power calculation indicated 21 patients in each group would have an 80% chance of detecting a difference of 15 mg of PCA morphine at the 5% level between groups of patients requiring high or low current to stimulate movement. There was no correlation between current, PCA morphine use or pain scores by linear or logistic regression analysis.

Although a nerve stimulator may help identify the position of a nerve, we have found no relationship between the minimum current required to elicit muscle contraction and PCA morphine consumption, or perception of pain after surgery (Table 17). The absolute value of current may be less important than clinical observation of the correct muscle movement.

Table 17 Pearson correlation coefficients, n=48

	PCA morphine in 24 h	Recovery - pain at rest	Recovery - pain on movement score for 24 h	Patients' pain
Femoral current	0.02	−0.05	−0.07	0.00
Sciatic current	0.17	0.24	0.19	0.10
Sum of currents	0.11	0.18	0.13	0.08

Keywords: nerve, stimulation; anaesthesia, regional

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Ciliary abundance and abnormalities in critical illness

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Mucociliary clearance is known to be impaired in the critically ill.[1] Abundance and ultrastructure of respiratory cilia are important determinants of efficient mucus clearance. Work in this area is limited, a previous study by Konrad *et al.* reported reduced mucus transport and ciliary abundance but no change in the prevalence of ultrastructural abnormalities during days 1–3 of intensive care.[2]

This study assessed ciliary abundance and ultrastructure in 20 intensive care patients: 13 males, 7 females; 22–84 (62) yr; length of stay 1–28 (8) days; admission APACHE II score 6–27 (17); range (median). Six patients subsequently died in hospital. Cytological brushings were taken blind from the trachea for transmission electron microscopy (TEM). Small forceps were used to take biopsies from the first division of the main bronchi. TEM was used to quantify the incidence of ciliary abnormalities in at least 500 cilia per patient taken from ten separate areas. The

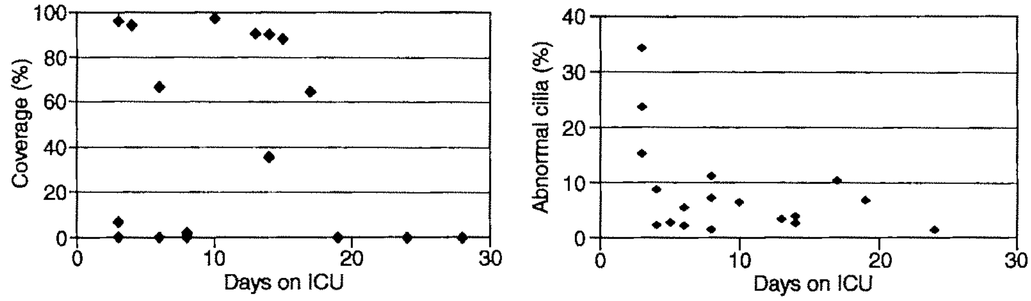

Fig 11 Cilial abundance and abnormalities in intensive care patients. Each data point represents one subject.

mucosa of biopsies was imaged by scanning electron microscopy (SEM), digitally capturing the largest area possible whilst avoiding any areas of mechanical damage. Standard software were used to quantify ciliary abundance in terms of percentage coverage. The laboratory researchers were blind to patient identity, diagnosis and duration of stay.

There is great variability in ciliary abundance and levels of abnormality within ICU patients (Figure 11). A large proportion has substantial abnormalities. There is no clear link between length of ICU stay and reduced abundance or incidence of abnormality.

Keywords: lung, trachea, respiratory cilia; intensive care

Acknowledgements

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POSTER PRESENTATIONS

Iontophoretically applied lidocaine to produce analgesia prior to Tuohy needle insertion

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Pain on injection of subcutaneous local anaesthetic is a recognized problem. Iontophoresis of lidocaine is an accepted technique to produce dermal anaesthesia.[1] [2] It is a painless technique that is well tolerated.[3] The aim of this study was to compare iontophoretically applied lidocaine with conventional local anaesthetic infiltration in providing analgesia prior to localization of the epidural space with a 16G Tuohy needle.

Eighteen ASA I–II women undergoing elective Caesarean section were recruited. The patients were allocated randomly to have either active or passive iontophoresis applied to the proposed site of epidural insertion. The active iontophoresis group received 4% lidocaine 1.5 ml by iontophoresis followed by local infiltration of 3 ml of normal saline. The passive iontophoresis group received 1.5 ml of normal saline by iontophoresis followed by local infiltration of 3 ml of 2% lidocaine. An independent blinded observer collected verbal analogue scores (VRS) [0–10] for pain associated with iontophoresis application, raising a skin bleb, local infiltration and Tuohy needle insertion. We also recorded the depth of the epidural space, any additional local anaesthetic required and the depth at which pain occurred. Statistical analysis was done by the Mann–Whitney U test and Chi-Squared test. $P<0.05$ was accepted as statistically significant.

Both groups were well matched for age height and weight. The median (range) VRS are shown in Table 18.

There was no difference between the two groups in the requirement for additional local anaesthetic or the depth at which pain was felt.

We conclude that iontophoretic application of 1.5 ml of 4% lidocaine is painless and is as effective as local anaesthetic infiltration with 3 ml of 2% lidocaine in providing analgesia for locating the epidural space.

Keywords: anaesthetics local, lidocaine; anaesthetic techniques, regional, iontophoresis

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Ethnicity and obstetric outcome

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Northwick Park has an annual delivery rate of around 4000 per annum. The population is multiethnic. There are large Asian and Somali communities each with their own particular health problems. There are very little data available on the ethnic variations in anaesthetic obstetric care in the United Kingdom.

The St Mary's Maternity Information System (SMMIS) has been in use in our hospital since 1987. Midwives collect baseline data on each parturient routinely and the anaesthetic personnel enter data on anaesthetic interventions and outcome into the anaesthetic module of the system. We examined the data base for primigravidae who delivered from 1997–1999 inclusive and examined it on the basis of racial group. Data were collected on 4595 mothers with ages ranging from 14 to 44 yr. There were 13 different racial classifications which were combined into five larger groups (group size ranging from 94 to 2143): White, Oriental, Asian, Afro-Carribean and Black other (mainly Somali).

Table 18 Comparison of active and passive iontophoresis. *$P<0.05$

	VRS Iontophoresis	VRS Skin bleb	VRS Skin infiltration	VRS Tuohy needle insertion	Overall VRS
Active Iontophoresis	0 (0–4)*	2 (0–3)*	2(0–8)	5 (3–9)	5 (4–7)
Passive Iontophresis	2 (0–5)	3 (2–8)	4(1–9)	4 (0–8)	4.5 (2–7)

Table 19 Incidence of different modes of delivery for the five patient groups

Delivery mode	Whites	Oriental	Asian	Afro-C	Black other
n	2143	94	1334	495	531
SVD & low forceps	1247	54	822	318	313
Ventouse & Keillands	404	19	232	51	86
Emergency LSCS	391	16	245	111	113
Elective LSCS	101	5	35	15	19

We looked at mode of delivery, Caesarean section rate and spontaneous vaginal delivery rate after epidural.

Data were analysed using contingency tables with correction for small numbers. The results are shown in the Table 19. There was a significant influence of ethnic group on mode of delivery (χ^2=37.88, P=0.0016) and epidural rate (χ^2=23.79, P=0.00024).

This study shows that ethnic group may have an influence on epidural rate and mode of delivery but other confounding variables need to be excluded.

Keywords: ethnic origin; anaesthesia, obstetric

First administration to man of ORG25435, a new intravenous anaesthetic agent

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Following preliminary animal experiments[1] and appropriate toxicology, we have evaluated the safety and efficacy of ORG25435, a novel water-soluble anaesthetic.

Male volunteers aged 26.2 (4.5) yr (mean (SD)) weighing 74.5 (8.2) kg received 0.25, 0.5, 1, 2, 3 or 4 mg kg^{-1} of ORG25435 over 1 min by i.v. infusion (n=2, 2, 2, 2, 5 and 5 respectively). In addition to standard anaesthetic monitoring, we recorded direct arterial blood pressure, EEG, trans-thoracic impedance cardiac output and video images. Appropriate blood samples were collected for pharmacokinetic analysis and biochemical and haematological safety data.

All subjects receiving 2 mg kg^{-1} became briefly drowsy: 3 mg kg^{-1} over 1 min caused loss of speech (at 45 (9) s after start of infusion), eye closure (54 (10) s), syringe drop (60 (13) s) and loss of lash reflex (65 (9) s) with eye opening to command at 240 (58) s; 4 mg kg^{-1} over 1 min caused loss of speech (at 39 (6) s), eye closure (43 (3) s), syringe drop (54 (11) s) and loss of lash reflex (69 (13) s) with eye opening to command at 341 (138) s. Small excitatory movements were observed in 6 of the 10 subjects receiving 3 or 4 mg kg^{-1}, predominantly in the hand gripping a water filled syringe. Clinically significant excitation was not observed. Peak EEG effect occurred during the infusion, within 1 min with increased theta and delta activity. Emergence from anesthesia was rapid and clear-headed. No subject experienced nausea or vomiting. Biochemistry and haematology were unchanged. Average changes in mean arterial blood pressure (MAP) were −4, 0, −4 and −5 mm Hg at 1, 2, 5 and 10 min after 3 or 4 mg kg^{-1}, greatest rise +15 mm Hg, greatest decrease −25 mm Hg. Heart rate (HR) increased after administration of ORG25435, Figure 12.

ORG25435 is an effective IV anesthetic in man with rapid onset of and recovery from anesthesia.

Keywords: anaesthetics i.v., ORG25435

Acknowledgement

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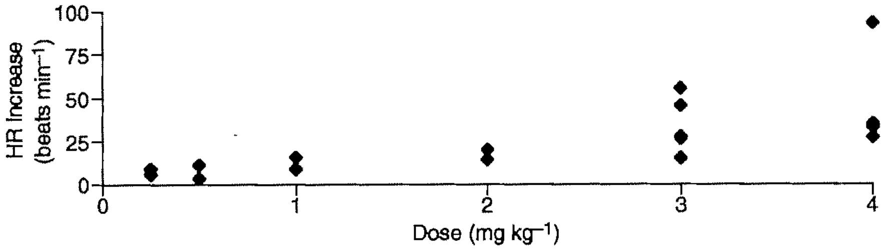

Fig 12 Maximum increase in HR during minutes 1–10 after starting administration of ORG25435. Data points are maximum HR minus baseline. Some data points overlap.

Buprenorphine disposition in the cat: a comparison with morphine following intravenous and intramuscular dosing

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Although the disposition of buprenorphine has been described in awake and anaesthetized patients with normal renal function and in patients with renal failure,[1 2] there are few data relating to its use in animal species. In the present study, we have examined the disposition of buprenorphine in cats by two dosing routes and compared the data with that for morphine.

Ten cats (ages 2–11 yr, weight 2.9–4.4 kg) received either buprenorphine (10 µg kg^{-1}) by i.v. dosing over 5–10 s (n=5) or by i.m. injection into the epaxial muscle (n=6), or morphine (0.2 mg kg^{-1}) by i.v. (n=6) or i.m. dosing (n=4) as part of a study examining the effects of opiates on thermal and mechanical threshold stimuli.[3] Cats were dosed in random order with at least 2 weeks between studies when the same cat participated. Blood samples were withdrawn from a jugular vein catheter at 15 time points to 24 h. Plasma buprenorphine concentrations were measured using a double-antibody ^{125}I-labelled solid-phase RIA and morphine by HPLC. Concentration-time data were used to determine the area under the curve (AUC) and its first moment (AUMC); mean residence time (MRT); clearance (Clp); apparent volume of distribution at steady state (Vss) and elimination half-life ($T_{1/2}$). For both drugs, 100% bioavailability was assumed for the two routes of administration; derived kinetic parameters are shown as mean (SD).

Following i.m. dosing, the median (range) C_{max} and T_{max} values were 8.7 (3.6–11.8) ng ml^{-1} and 3 (2–15) min for buprenorphine, and 120 (45–218) ng ml^{-1} and 15 (1–45) min for morphine (Table 20). By both dosing routes, drug clearances were similar but buprenorphine had a larger V_{ss} and longer MRT and $T_{1/2}$ than morphine, reflecting its greater lipid solubility. These kinetic estimates are broadly similar to data from human studies.

Table 20 Disposition of buprenorphine and morphine by i.v. and i.m. dosing in cats (mean (SD)). Clp: ml kg^{-1} min^{-1}; MRT and $T_{1/2}$: minutes; Vss: litres kg^{-1}

	n	Clp	MRT	Vss	$T_{1/2}$
Buprenorphine					
intravenous	5	18.7 (4.1)	451.9 (130.3)	8.2 (2.0)	470.0 (133.5)
intramuscular	6	23.65 (12.65)	409.8 (154.8)	8.9 (5.9)	380.2 (131.0)
Morphine					
intravenous	6	24.1 (10.3)	105.0 (22.5)	2.6 (1.3)	76.3 (17.6)
intramuscular	4	13.5 (4.6)	120.5 (37.6)	1.7 (0.8)	93.6 (7.5)

Keywords: pharmacokinetics, buprenorphine

Acknowledgement

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Are subjects more easily aroused during sedation with the alpha$_2$ agonist, dexmedetomidine?

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For more than a decade alpha$_2$ agonists have been employed to provide preoperative sedation and anxiolysis and to decrease intra-operative anaesthetic requirements. Recently, its use for sedation has been explored in a multi-centre randomized clinical trial involving several hundred postoperative patients requiring mechanical ventilation.[1] Patients receiving dexmedetomidine required significantly less midazolam than placebo-treated patients for the same level of clinical sedation. In an assessment of 'ease of care' nurses subjectively described the patients as having a unique type of sedation in which they could be readily aroused and then returned to their sleep-like state when left alone. In this study we have objectively assessed whether the sedative state produced by midazolam differs qualitatively from that seen with dexmedetomidine.

Subjects (*n*=10) were sedated with either dexmedetomidine, midazolam, or placebo on consecutive weeks using a computer-controlled plasma target model. Attempts were made to sedate the subjects to the same behavioural end point as monitored by a combination of independent observer assessment and BIS scores. Once the desired level of sedation was achieved the subjects were asked to perform a visual recognition task. This task was performed under two conditions, either quiet with no distracting noise or under the influence of a non-descript white noise played at 80 dB via headphones. When the subjects recognized a certain simple combination of letters on a computer screen, they were asked to press a button. The response time and the percentage success rate were electronically recorded and the results analysed.

The data reveal that at 'equi-sedative' states there is a significant decrement in performance for both dexmedetomidine (62.5%) and midazolam (66.7%) treatments. Subjects sedated with dexmedetomidine demonstrated an improvement in their performance when studied in the presence of a distracting noise compared to midazolam (80.9%). In contrast, task performance was unaffected by noise in the midazolam-sedated state (71.2%).

These data reveal that attentiveness can be improved in the dexmedetomidine-sedated state during auditory stimulation. Thus, one may anticipate that patients sedated with alpha$_2$ agonists may be more co-operative and communicative than patients sedated with current strategies in the intensive care setting thereby facilitating nursing and medical care.

Keywords: analgesics, dexmedetomidine; sedation

Acknowledgement

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Potency estimation of rapacuronium using two different modes of nerve stimulation

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Rapacuronium is a new aminosteroid muscle relaxant with a rapid onset, a short duration of action, and possibility of early reversal using an empirically determined dose of 1.5 mg kg^{-1}.[1] Although this study showed that intubating conditions using this dose were similar to those of succinylcholine 1.0 mg kg^{-1}, subsequent studies under routine clinical conditions showed these to be not as good as those after succinylcholine. As there are no actual reports of the potency estimation of rapacuronium, it is possible that the dose used is not appropriate. The aim of the present study was to estimate the potency of rapacuronium. The influence of two different modes of nerve stimulation was also examined as previous studies have shown that this can influence the results.[2]

The study was performed under a DDX from the Medicines Control Agency. Forty-eight patients were included. They were anaesthetized with fentanyl 1–3 µg kg^{-1}, 66% nitrous oxide in oxygen and propofol 1–3 mg kg^{-1} followed by a propofol infusion. Neuromuscular block was monitored by stimulation of the ulnar nerve at the wrist and recording the force of contraction of the adductor pollicis muscle using a force displacement transducer and a neuromuscular function analyser. Single twitch (ST) stimulation at 0.1 Hz or a train-of-four (TOF) stimulation at 2.0 Hz every 10 s was used and about 10 min allowed for the control responses to stabilize. The skin temperature over the adductor pollicis muscle was maintained above 32°C by wrapping the arm in cotton wool. Six patients each were randomly allocated to receive 0.25, 0.5, 0.75, or 1.0 mg kg^{-1} of rapacuronium and to the ST or TOF modes of stimulation. The maximum block was allowed to supervene after each dose irrespective of the time taken

Table 21 ED_{50} and ED_{95} (95% confidence limits)

	Single twitch stimulation	**Train-of-four stimulation**
ED_{50} ($\mu g\ kg^{-1}$)	356 (304–418)	321 (284–363)
ED_{95} ($\mu g\ kg^{-1}$)	791 (674–928)	591 (523–667)

to attain it. The response data were arc-sine transformed, regression analysis carried out, dose-response lines constructed and ED_{50} and ED_{95} estimated. The dose-responses were subjected to analysis of covariance.

The degree of block increased in a dose-related manner with both modes of stimulation. Analysis of dose-response curves showed that these did not differ in their slopes but the separation between them was significant ($P<0.05$), the apparent potency being greater using the TOF mode of stimulation. The respective ED_{50}s and ED_{95}s are given in Table 21.

Keywords: neuromuscular block, rapacuronium; monitoring

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Respiratory response to skin incision during anaesthesia with propofol and alfentanil infusion

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The ventilatory response to skin incision during anaesthesia with enflurane is an increase in tidal volume without a change of frequency.[1] Because opioids have an obvious effect on frequency, we wondered if the breathing response to pain could be different during anaesthesia using opioids.

We recruited 12 ASA I patients (5 male, mean (range) age 46 (25–77) yr, mean (SD) weight 75 (9) kg) about to have varicose vein surgery. Anaesthesia was induced and maintained with intravenous infusions of propofol and alfentanil, from a Graseby Diprifusor (Zeneca) and an Ohmeda syringe driver controlled by a Psion II palmtop computer respectively. Initial target concentrations were 5 $\mu g\ ml^{-1}$ of propofol and 50 $ng\ ml^{-1}$ of alfentanil, adjusted between 4 and 6 and 40 and 60 respectively, in proportion, according to clinical requirements. After insertion of a laryngeal mask airway, the patients breathed 40% oxygen/air mixture from a T piece with a venturi mixing device, through a pneumotachograph (Mercury F10L) connected to a differential pressure transducer (Furness FC40) and a laptop computer with an A/D converter (Amplicon PC30G). Flow signals were converted into text files and processed using Microsoft Excel. Measurements were made of the three breaths before and the 20 s after the first skin incision. Data are expressed as fractions of the average of the three breaths before incision and summarized as median and interquartile values.

Data from one patient were not analysed because of slow breathing. In the others, minute ventilation increased after incision, with considerable individual variation in the response. Tidal volume increased promptly by 17 (4,81)%, the duration of inspiration was virtually unaltered, and the duration of expiration decreased more gradually by 5 (–1,8)% (Figure 13). Those patients who showed more response, showed more change in both these measures, so that there was a significant relationship between increased inspiratory flow rate and reduced expiratory time ($P<0.05$). We conclude that during opioid anaesthesia, the mechanism of ventilatory increase after stimulation involves changes in both drive and timing of breathing.

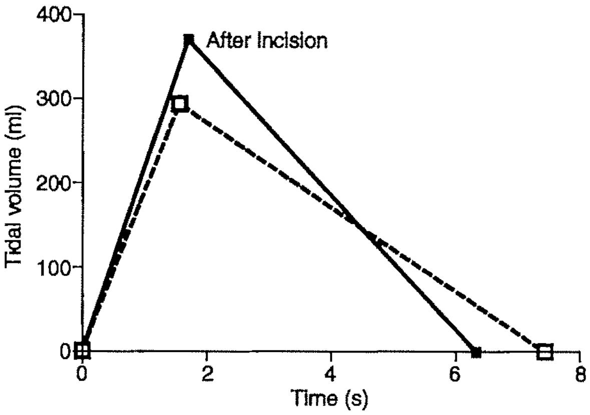

Fig 13 Idealized average breath before incision (dashed line) and five breaths after (solid line).

Keywords: anaesthetics, i.v.; ventilation

Reference

1 Sutherland RW, Drummond GB. *Br J Anaesth* 1996; **76**: 777–9

Fentanyl 25 μg i.v. given to patients breathing spontaneously during laparoscopy causes increases in abdominal pressure

M. K. Duncan* and G. B. Drummond

Department of Anaesthetics, Royal Infirmary, Edinburgh, UK

Phasic abdominal pressure changes during anaesthesia have been described.[1] [2] We routinely allow patients to breathe spontaneously during laparoscopy for gynaecological surgery, and noticed that abdominal pressure increases occurred when fentanyl was given.

We recruited 11 ASA I and II patients (mean (SD)) age 34 (8), range 18–45 yr, mean weight 65 (5) kg, height 165 (6) cm about to have laparoscopy. Anaesthesia was induced with propofol and sevoflurane. After insertion of a laryngeal mask airway, the patients breathed 1–2% isoflurane and 70% nitrous oxide from a circle system. After insertion of the trocar for the laparoscope, we connected a differential pressure transducer (Gaeltec 8T50) to a side connection on the gas inflation tube. A signal proportional to respired flow was measured (Furness FC10) from the pressure difference across a breathing circuit filter. At the end of the procedure, the insufflating gas flow was stopped and after the abdominal pressure became stable, fentanyl 25 μg were given i.v. Recording was continued for 2 min before the patient was allowed to recover from the anaesthesia. The signals were digitized using an A/D converter and associated Spike 2 software. Flow signals were converted into text files and processed using Microsoft Excel. Results are given as mean (SD).

Peek abdominal pressure increased from 17 (5) to 25 (9) cm H_2O. Respiratory rate decreased from 32 (8) to 23 (7) breaths min^{-1} (Figure 14) and PE'_{CO_2} increased from 5.4 (0.7) to 6.0 (0.7) kPa. End-tidal isoflurane concentration was 1.2 (0.3) before and 1.1 (0.2) after fentanyl.

We conclude that fentanyl 25 μg increases intra-abdominal pressure in spontaneously breathing patients, probably by activation of the abdominal muscles.

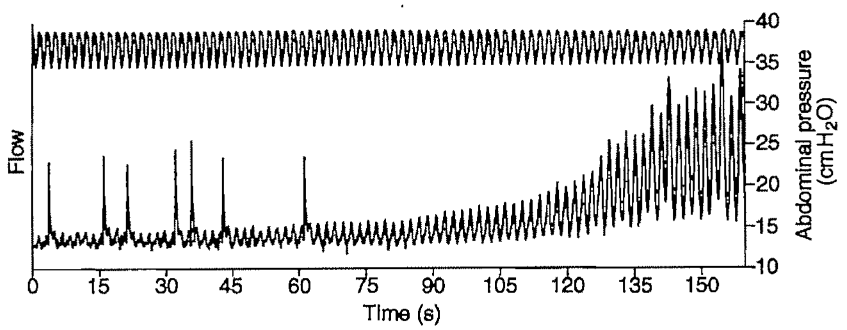

Fig 14 Representative trace of flow (upper) and abdominal pressure (lower trace) (cm H_2O, right axis). Fentanyl 25 µg given at 30 s.

Keywords: analgesics opioid, fentanyl; surgery, laparoscopy

References

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Abnormalities of respiratory cilia in non-symptomatic smokers and non-smokers

J. Kirkby[1]*, R. Kay[1]*, J. A. Langton[2], S. Loxdale[2]*, R. Moate[1]*, and J. R. Sneyd[2]

[1]Electron Microscope Unit, University of Plymouth and [2]Department of Anaesthesia, Derriford Hospital, Plymouth, UK

Cigarette smoking increases the risk of respiratory infections in the post-operative period and in intensive care.[1] Studies comparing ultrastructural abnormalities in smokers and non-smokers have yielded conflicting results.[2–4]

Tracheal brushings were collected from 50 healthy smokers (7 males, 16 females) and non-smokers (6 males, 21 females) after induction of anaesthesia (propofol, fentanyl, isoflurane, N_2O) for day surgery. Ciliary orientation and incidence of ciliary abnormalities were quantified by transmission electron microscopy (TEM) analysis of transverse cross-sections taken from at least five separate areas. Laboratory researchers were blind to patient details. A minimum of 500 cilia were examined from each patient. In an arbitrary sub-set of 30 patients cilial orientation was determined by measuring the alignment of the central tubules in ⩾10 cilia in each of 10 images from each patient.[5] The extent of disorientation in each patient was quantified as the standard deviation of the angles of alignment.

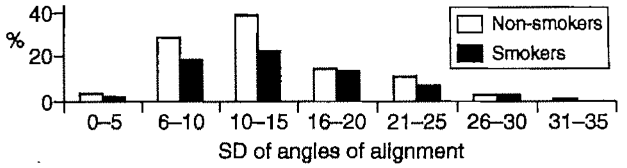

Fig 15 Cilial orientation (SD of angles of alignment) showing no significant difference between the groups (nested ANOVA, P=0.45)

The proportions of abnormal cilia in the smokers and non-smokers were 3.21% (median 2.77, range 0.52–8.37) and 3.05% (median 2.89, range 0.76–7.21), respectively. There was no significant difference between the groups (P=0.996, unpaired t-test after logit transformation). None of the patients' cilia could be classified as grossly disorientated and the variation of cilial orientation in the two groups were similar (Figure 15).

We were unable to demonstrate any difference in ultrastructural abnormalities or cilial orientation between asymptomatic smokers and non-smokers.

Keywords: lung, trachea, respiratory cilia; complications, smokers

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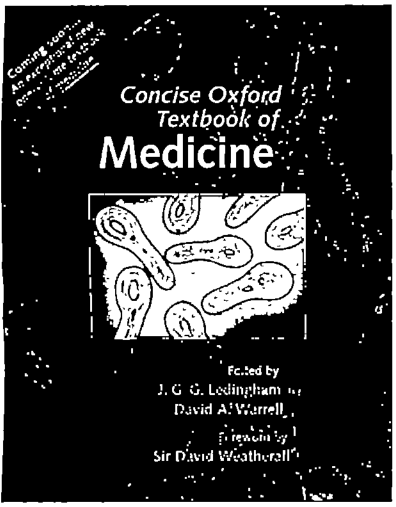

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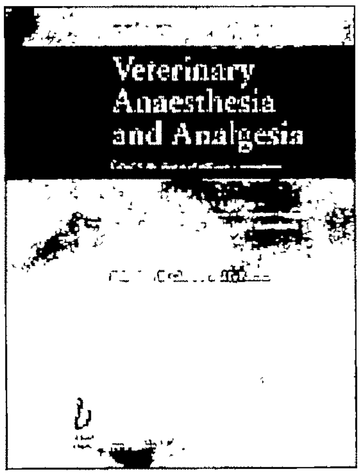

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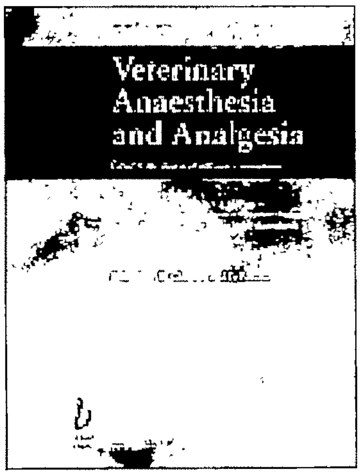

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BJA
International Journal of Anaesthesia
Volume 86 Number 3 March 2001

EDITORIALS

327 I. Right heart catheterization in intensive care
J. D. Young

329 II. Codeine phosphate in children: time for re-evaluation?
M. Cunliffe

CLINICAL INVESTIGATIONS

332 Dose-dependent prophylactic effect of nicorandil, an ATP-sensitive potassium channel opener, on intra-operative myocardial ischaemia in patients undergoing major abdominal surgery
T. Kaneko, Y. Saito, Y. Hikawa, K. Yasuda and K. Makita

338 Prediction of volatile anaesthetic solubility in blood and priming fluids for extracorporeal circulation
R.-G. Yu, J.-X. Zhou and J. Liu

345 Compound A production from sevoflurane is not less when KOH-free absorbent is used in a closed-circuit lung model system
L. Versichelen, M. P. Bouche, M. Struys, J. Van Bocxlaer, E. Mortier, A. P. de Leenheer and G. Rolly

349 Arterial to end-tidal carbon dioxide tension difference in children with congenital heart disease
J. A. Short, S. T. Paris, P. D. Booker and R. Fletcher

354 Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane
K. Kuizenga, J. M. K. H. Wierda and C. J. Kalkman

361 Recovery from propofol anaesthesia supplemented with remifentanil
R. A. O'Hare, R. K. Mirakhur, J. E. Reid, D. S. Breslin and A. Hayes

366 Post-operative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurane and spinal anaesthesia
J. M. Williams, P. A. Stoddart, S. A. R. Williams and A. R. Wolf

372 Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during Caesarean section
B. T. Ayorinde, P. Buczkowski, J. Brown, J. Shah and D. J. Buggy

377 I.V. ketoprofen for analgesia after tonsillectomy: comparison of pre- and post-operative administration
A. Salonen, H. Kokki and K. Tuovinen

382 Analysis of the French health ministry's national register of incidents involving medical devices in anaesthesia and intensive care
L. Beydon, F. Conreux, R. Le Gall, D. Safran, J. B. Cazalaa and the members of the 'Sous-commission de Materiovigilance' for Anaesthesia and Intensive Care

LABORATORY INVESTIGATIONS

388 Differential nitric oxide synthase activity, cofactor availability and cGMP accumulation in the central nervous system during anaesthesia
H. F. Galley, A. E. Le Cras, S. D. Logan and N. R. Webster

395 Suppressive effect of nitrous oxide on motor evoked potentials can be reversed by train stimulation in rabbits under ketamine/fentanyl anaesthesia, but not with additional propofol
T. Sakamoto, M. Kawaguchi, S. Inoue and H. Furuya

403 Evaluation and comparison of the pharmacokinetic and pharmacodynamic properties of allopregnanolone and pregnanolone at induction of anaesthesia in the male rat
D. Zhu, M. D. Wang, T. Bäckström and G. Wahlström

REVIEW ARTICLE

413 Codeine phosphate in paediatric medicine
D. G. Williams, D. J. Hatch and R. F. Howard

SHORT COMMUNICATIONS

422 Predicted effect compartment concentration of thiopental at loss of eyelash reflex
T. A. Lim and K. Inbasegaran

425 Effects of hypoxia and isoflurane on liver blood flow: role of adenosine
S. H. Cray, M. W. Crawford, N. Khayyam and F. J. L. Carmichael

427 Heterogeneous distribution of cardioplegic solution in pigs
J.-S. Han, D.-M. Soh, C.-W. Joh, B.-I. Choi, Y.-S. Lee, C.-J. Lee and C.-H. Park

CASE REPORTS

431 Liver transplantation for massive hepatic haemangiomatosis causing restrictive lung disease
M. T. Keegan, G. S. Kamath, G. M. Vasdev, J. Y. Findlay, G. J. Gores, J. L. Steers and D. J. Plevak

435 Undiagnosed cardiomyopathy in a neonate: significance of low oxygen saturation during anaesthesia
W. Q. Smith and M. Abu-Harb

437 Multiple acyl-CoA dehydrogenase deficiency: a rare cause of acidosis with an increased anion gap
A. S. Grice and T. E. Peck

442 Subarachnoid haemorrhage following spinal anaesthesia in an obstetric patient
S. M. Eggert and K. A. Eggers

COMMENTARY

445 Assessment instruments used during anaesthetic simulation: review of published studies
A. J. Byrne and J. D. Greaves

451 CORRESPONDENCE

460 BOOK REVIEWS

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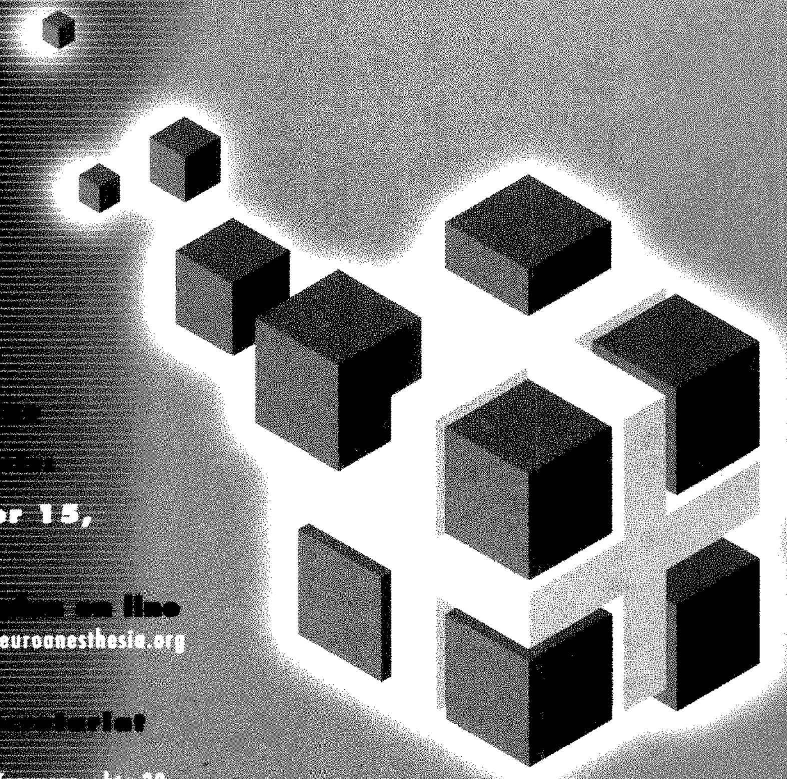

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To qualify, the principal applicant must be a member of the European Academy of Anaesthesiology (EAA) and be an investigator with a research record who has yet to establish a history of substantial funding. The award will go to a research project, which is judged by peer review to have high scientific merit and high probability of success. Priority funding will be awarded to proposals which are independent of other grant support. Experienced investigators working in new areas will receive consideration. The proposed project must have direct relevance to the speciality of anaesthesiology. Applicants must submit their curriculum vitae as well as an outline of their proposed research project. Furthermore, the application should be accompanied by a letter from the chairman of the department outlining the applicant's research qualities.

2. EAA Teaching Recognition Award

The purpose of this award is to discover an individual with outstanding teaching skills besides his/her research skills. The award winner will be required to give a total of five lectures. One lecture must be presented at the annual EAA congress. The other four lectures will be given in each of four different European countries, either at university departments or at the annual congress of the national societies. The award winner will receive a travel reimbursement for every lecture up to 1250 Euro. The remaining travel expenses will be paid by the host departments or congress organizers, if necessary. The maximum amount to be awarded is 5000 Euro.

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3. EAA Training Award

This award is created for young anaesthetists, including residents in their last year of training, with the aim of completing their training in another European department of anaesthesiology, recognized as a European centre for training of anaesthesiologists. The winner of the award will receive 2000 Euro per month for a maximum of six months.

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Please submit one original application and six copies to the EAA Secretary, **before April 30, 2001.** Prof. Dr. Th. Pasch, UniversitatsSpital Zürich, Direktor des Institut für Anästhesiologie, Rämistraße 100, CH-8091 Zürich, Switzerland.

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For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

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March 16–20, 2001

IARS 75th Clinical and Scientific Congress, Convention Center, Ft. Lauderdale, Florida, USA.

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

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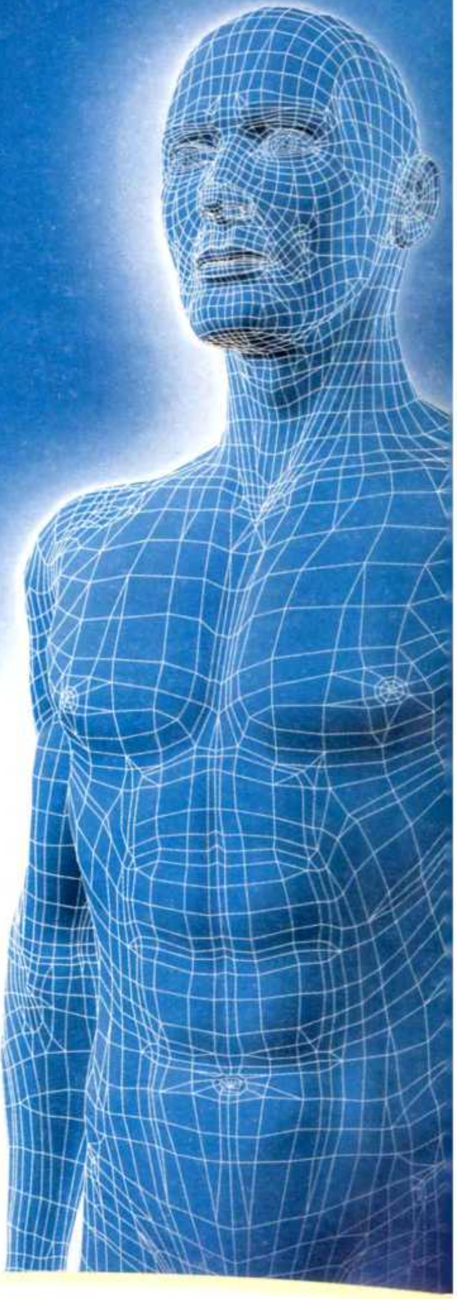

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For further information on the meeting please visit our website: www.nas.dundee.ac.uk or contact: Conference Secretary (NAS 2001), Department of Anaesthesia, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. Tel: +44 1223 217897; Fax: +44 1223 217223; E-mail: christine.butler@msexc.addenbrookes.anglox.nhs.uk

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Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

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Royal Lancaster Hotel, London, England, May 31–June 2, 2001

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German Congress of Anaesthesiology 2001 (DAK 2001)

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For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

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Abstracts deadline: May 15, 2001

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Durban, South Africa, September 22–23, 2001

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Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

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8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

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20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

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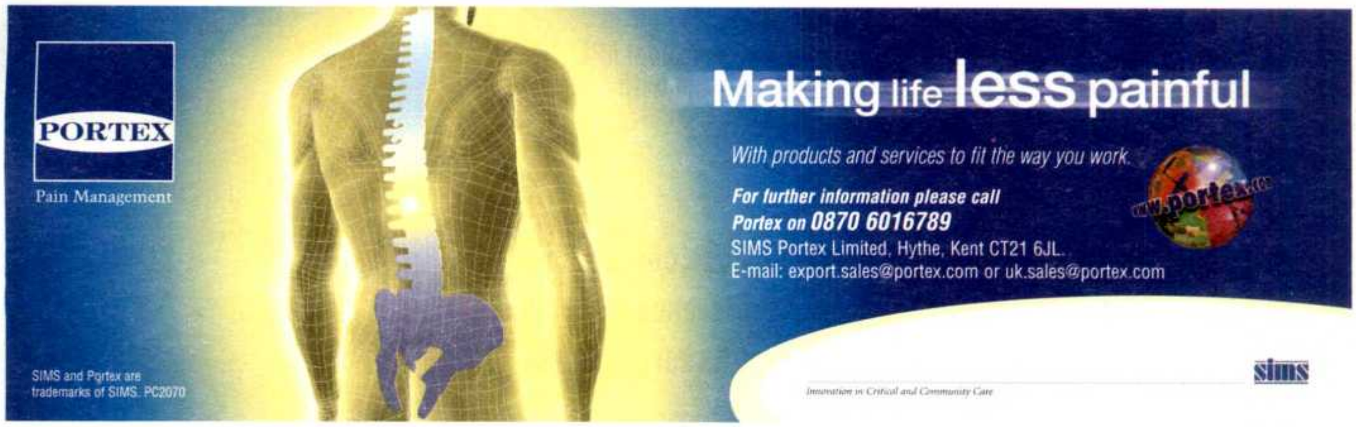

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Messezentrum Nürnberg, June 18–21, 2003

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Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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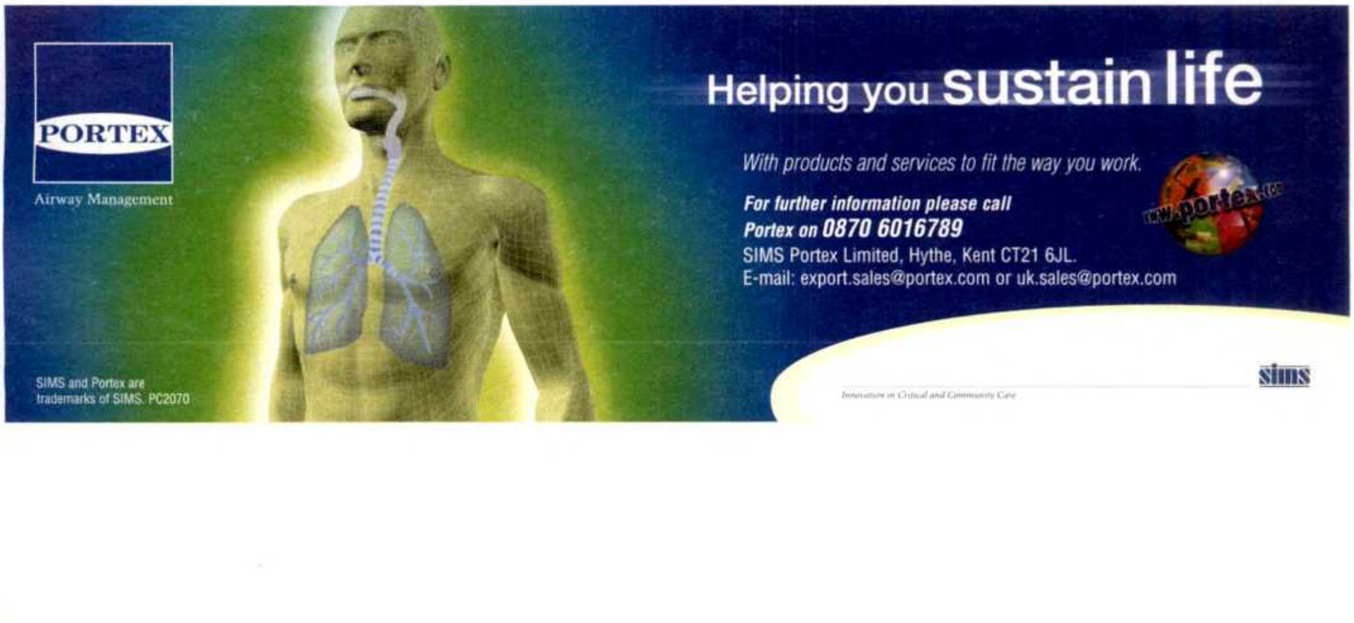

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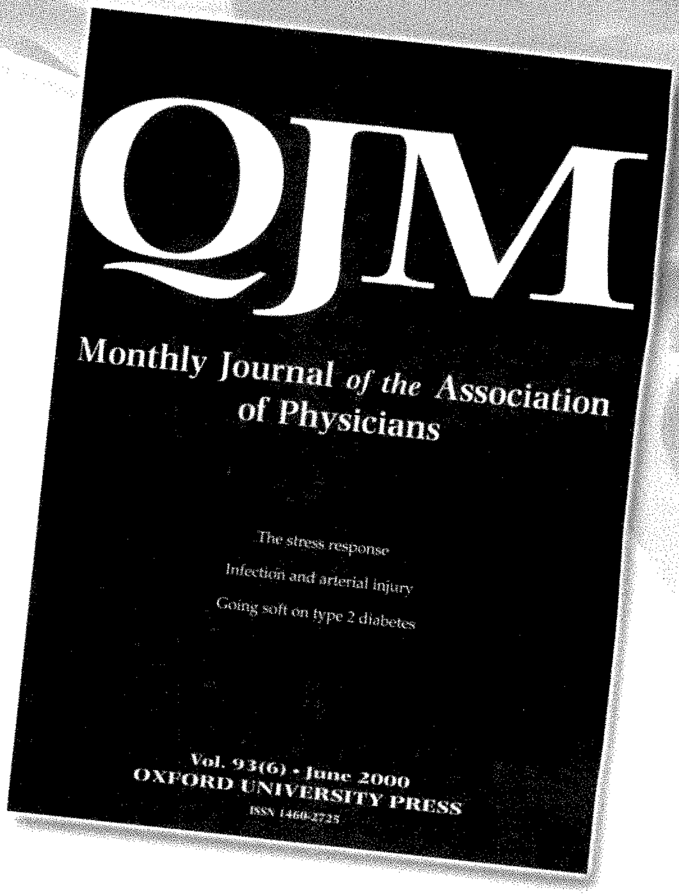

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Infection and arterial injury
Going soft on type 2 diabetes

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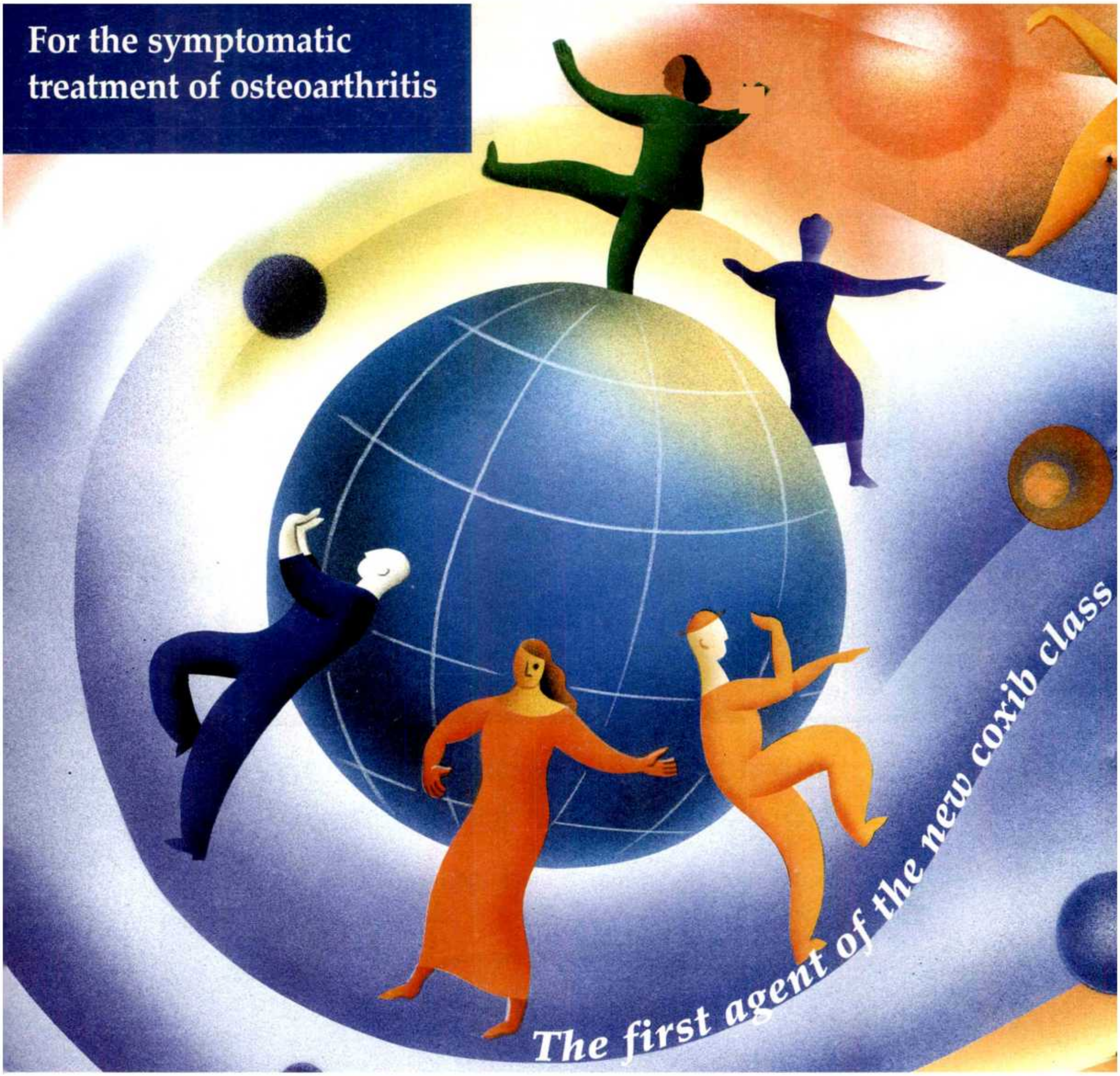
Abbreviated Prescribing Information
Moraxen® 35, 50, 75 and 100. Morphine® Sulphate 35, 50, 75 and 100mg. Please refer to SmPC before prescribing. **Indication:** For the short-term treatment of severe pain in advanced cancer when the oral route is no longer feasible for administering morphine. **Dosage and Administration:** Non dissolving suppository for rectal administration. Each Moraxen® unit should be inserted through the anus into the rectum. Up to two units may be inserted together, by applying a small amount of aqueous gel to each unit and the anal sphincter, to provide the following dosages 35, 50, 70, 75, 85, 100, 110, 125, 135, 150, 175 and 200mg. The dose conversion between 24-hour oral morphine and Moraxen® is 1:1. After approximately 24 hours Moraxen® should be expelled and replaced with another Moraxen® to continue pain management. If Moraxen® is lost prematurely due to defecation, a new Moraxen® should be inserted immediately. **Contra-indications:** Known sensitivity to morphine, morphine salts or hydrogel polymer components, respiratory depression, obstructive airways disease, acute hepatic disease, paralytic ileus, acute abdomen, diarrhoea, concurrent administration of monoamine oxidase inhibitors (MAOIs) or within two weeks of their discontinuation, head injuries, potential for raised intracranial pressure, painful conditions of the rectum or anus, neutropenia (<500 neutrophils/mm3) and in children aged 18 years or younger. In patients with rectal tumours producing excess mucus caution should be observed. **Warnings and Precautions:** Administer with caution in the elderly or debilitated, in severe renal or hepatic insufficiency, Addison's disease, myxoedema, hypothyroidism, prostatic hypertrophy, urethral stricture, hypotension associated with hypovolaemia, disease of the biliary tract, pancreatitis, inflammatory bowel disease, CNS depression, toxic psychosis, acute alcoholism, delirium tremens and convulsive disorders. Use in pregnancy only if the need for strong opioid analgesia justifies the potential risk to the foetus. **Undesirable effects:** Serious adverse reactions include respiratory depression and arrest, apnoea, circulatory depression, cardiac arrest, hypotension and/or shock. The most frequent less severe side effects include constipation, lightheadedness, dizziness, sedation, nausea, micturition disturbances, biliary colic, ureteric spasm, vomiting, sweating, dysphoria euphoria, dry mouth, headache, facial flushing, mood changes, palpitations, hallucinations, bronchospasm, colic, urticaria and pruritus. Rectal erythema and bleeding and anal irritation have been described in some patients. **Pack Quantities and Basic NHS Cost:** Blister packs of 7 units: £10.00 (35mg), £10.50 (50mg), £15.75 (75mg), £21.00 (100mg). **Legal Category:** POM, CD. **Product Licence Number:** PL 11937/0009 (35mg), PL 11937/0010 (50mg), PL 11937/0011 (75mg), PL11937/0007 (100mg). **Product Licence Holder:** CeNeS Drug Delivery Limited, Riverside Way, Riverside Business Park, Irvine KA11 5DJ, Scotland, United Kingdom. **Distributor (UK):** Schwarz Pharma Ltd., East Street, Chesham, Buckinghamshire, HP5 1DG, United Kingdom. Further information is available from: Schwarz Pharma Ltd., Schwarz House, East Street, Chesham, Buckinghamshire HP5 1DG (Telephone 01494 797 500). (1657). **Reference: 1.** Davis C. The role of a new 24-hour morphine hydrogel suppository (MHS) in palliative care. Eur J Palliat Care (In Press). **Date of preparation:** August 2000. (1644)

SCHWARZ
PHARMA

For the symptomatic treatment of osteoarthritis


The first agent of the new coxib class

VIOXX®▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib.

VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

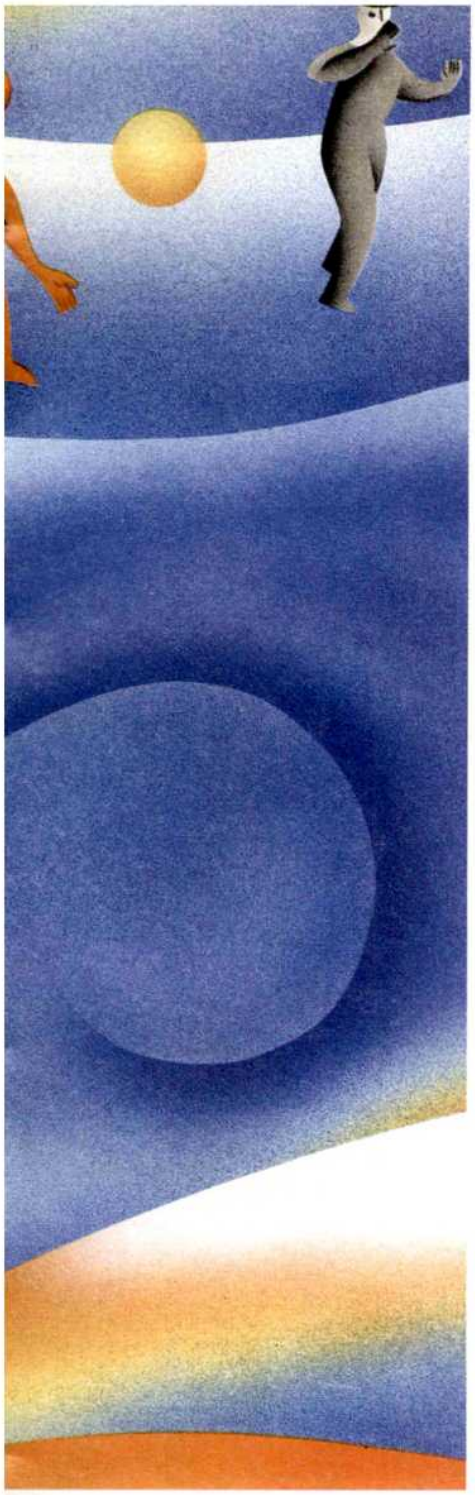
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1]*

- The power of high-dose NSAIDs – diclofenac and ibuprofen.[2]
- Superior GI safety profile compared to conventional NSAIDs – diclofenac, ibuprofen and nabumetone.[2,3]
- True once-daily therapy – for a wide range of patients.[2]

* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

TRUE ONCE-DAILY

VIOXX® ▼

(rofecoxib)

Selective. Strong. Simple.

rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** May 2000.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastro-intestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

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Date of preparation: February 2000

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References:
1. Stowell CP, Chandler H, Jove M, Guilfoyle M, Wacholtz MC. *Orthopedics*. 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop*. 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics*. 1999;22(suppl 1):s119-s128.

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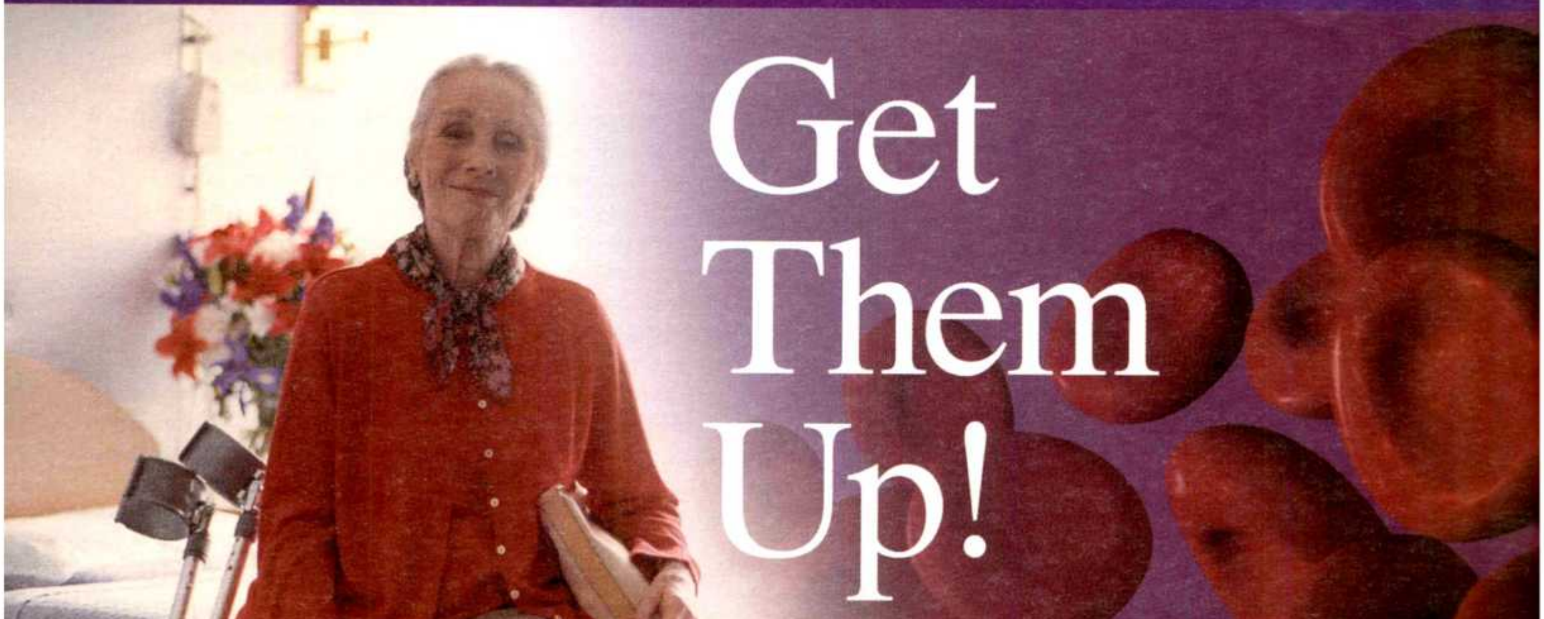

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Abbreviated version of the international summary of product characteristics Therapeutic Indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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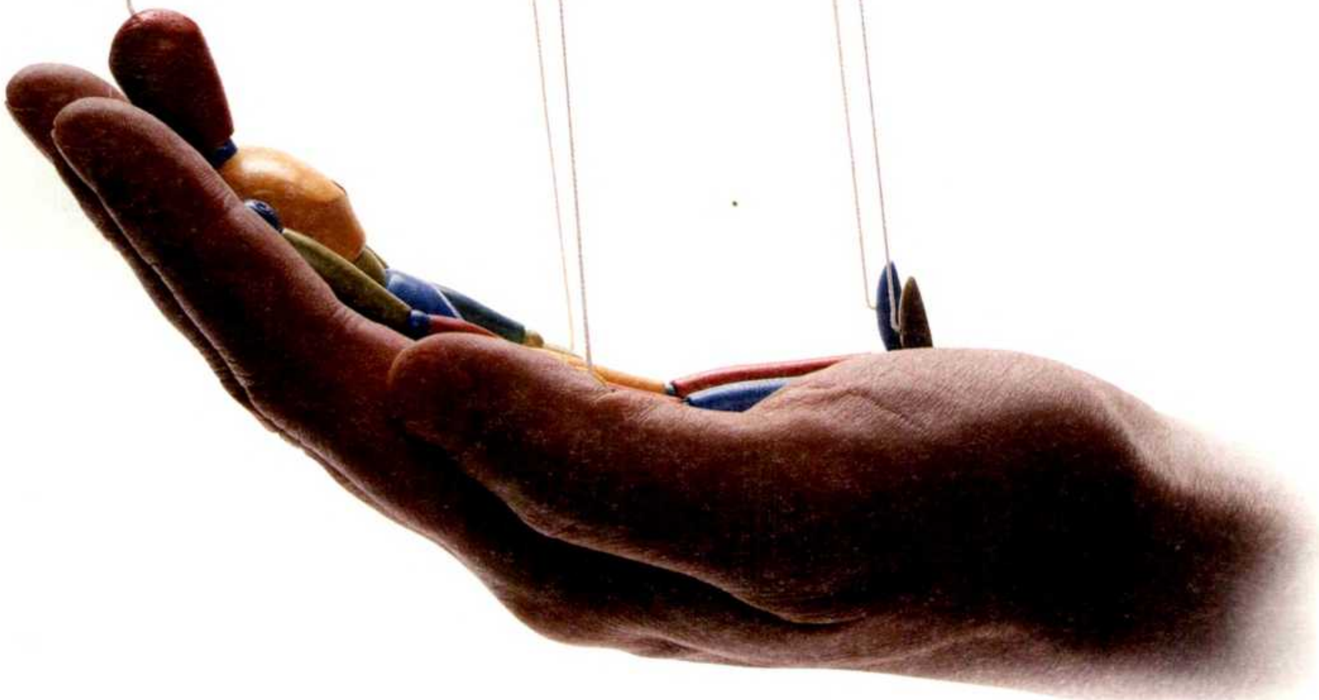

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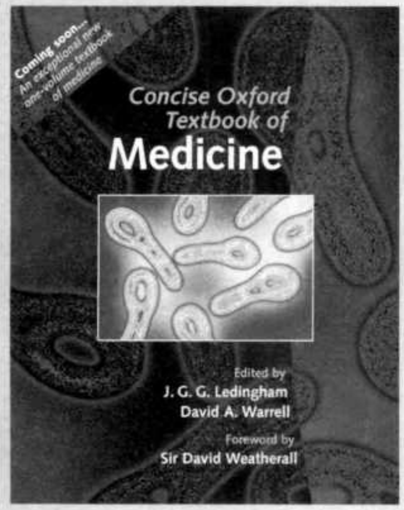
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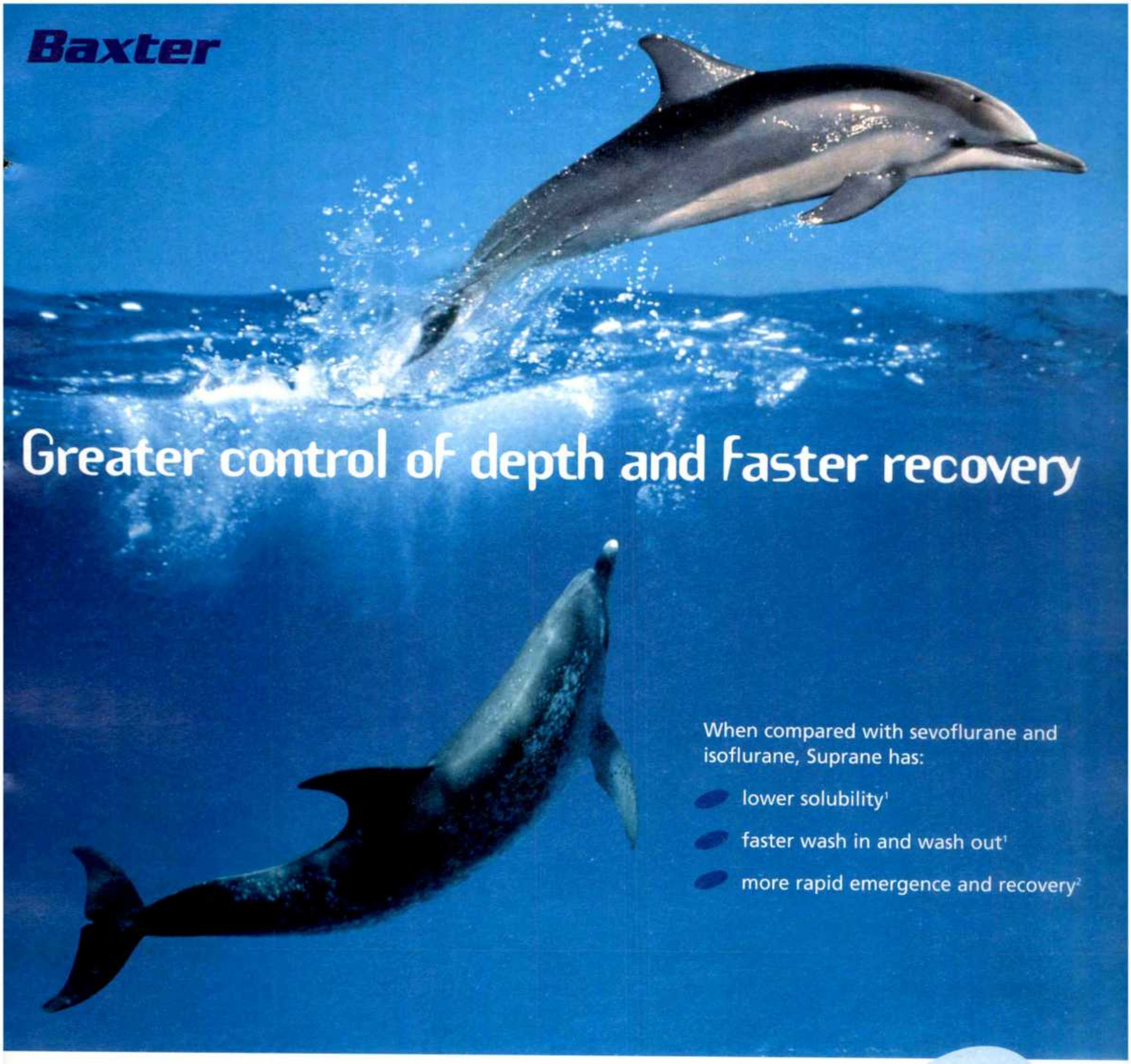
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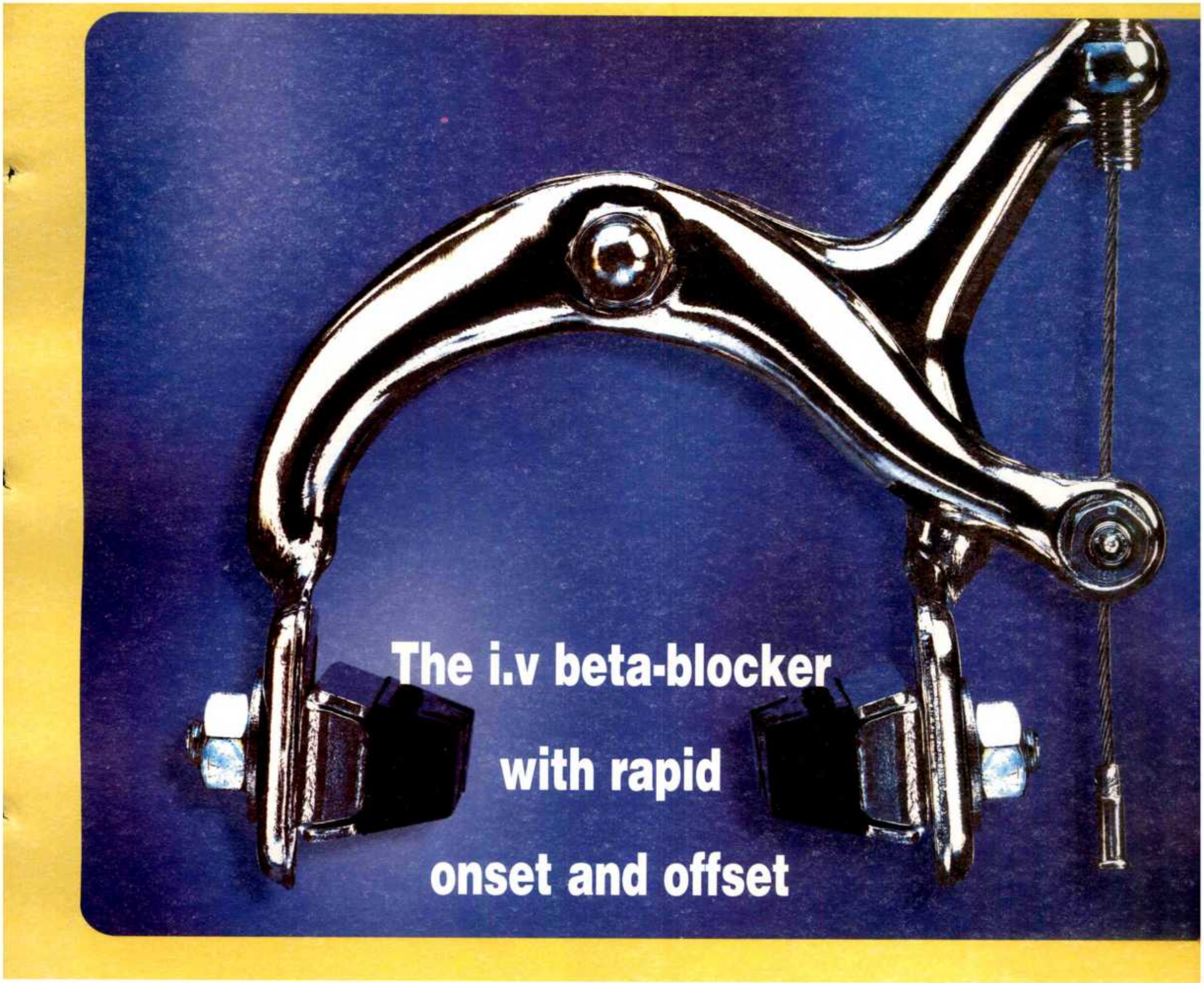

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Editorial I

Right heart catheterization in intensive care

On All Fools Day, 1949, the *Journal of Applied Physiology* received a manuscript from Hellems and colleagues describing the indirect measurement of left atrial pressure in man using occlusion of a small branch of the pulmonary artery.[1] In the half century since this publication, the pulmonary artery wedge pressure has been used in the cardiac catheter laboratory by generations of cardiologists to diagnose and assess the severity of congenital and acquired cardiac disease and to appropriately select patients for surgical correction. Twenty-one years later, in 1970, Swan and colleagues described similar measurements made using a balloon-tipped flow-directed catheter.[2] This development moved the right heart catheter out of the cardiac catheterization laboratory and up to the bedside. Continuous bedside monitoring of haemodynamic variables extended the scope of right heart catheterization beyond simple diagnosis, as manipulation of the various haemodynamic variables for presumed therapeutic benefit became a practical proposition. The best example of this haemodynamic variable-driven therapy is the 'goal-directed therapy' developed by Shoemaker in 1982.[3] For the past 20 years, the package of right heart catheter insertion, and measurement of haemodynamic variables and their subsequent manipulation has been taught to every resident in critical care.

The development and subsequent acceptance of right heart catheterization by the critical care community paralleled another far more important and globally applicable development in medical science. The publication of the 1948 Medical Research Council report on the treatment of pulmonary tuberculosis with streptomycin,[4] is generally considered to mark the birth of the modern randomized controlled trial (RCT). Like the right heart catheter, the use of the controlled trial as a clinical research tool has increased exponentially over the last 50 years, becoming totally accepted by the 1980s. If bedside right heart catheterization were developed today it would probably not be accepted without evidence from an RCT indicating that it reduced mortality, morbidity, length of stay or the cost of health care. Yet, because of its coincidence with the birth of the RCT, it escaped this formal evaluation and as a result unequivocal evidence for its benefit does not exist.

In 1996, Cooper and colleagues systematically evaluated all the available evidence for benefit from pulmonary artery catheterization.[5] Of the 543 studies they identified, only one was considered 'level I' evidence (large randomized trial with low risk of false positive or false negative errors). This was a trial of goal-directed therapy conducted in Italy by Gattinoni and colleagues,[6] which showed no difference between treatment and control groups. There was weak level II evidence (small trials, high risk of errors) outside intensive care showing a benefit for right heart catheterization in the pre- and intra-operative care of some high risk surgical patients. They concluded that, for a mixed ICU population, there was currently no proof of benefit for the use of right heart catheterization but also no proof that its use was harmful.

The concept that there might be mortality attributable to or associated with the use of right heart catheterization had been proposed for patients with myocardial infarction, where those patients receiving right heart catheters had a higher mortality (see for instance Gore and colleagues[7]). However, the studies were simple case series, so it may be that the more severely afflicted patients received the right heart catheters. The first major attempt to deal with the confounding effects of case mix was published by Connors and colleagues in 1996.[8] They performed a retrospective analysis of prospectively gathered data from a multi-centre study of decision making in critically ill adults (the SUPPORT project). A total of 2016 patients were included, of which 80% had acute respiratory failure or multi-system organ failure (MSOF); the remainder had chronic obstructive pulmonary disease, chronic heart failure, cirrhosis, non-traumatic coma, metastatic colonic cancer or lung cancer. A 'propensity score' was developed to determine the probability of right heart catheterization and patients who had received a right heart catheter in the ICU within 24 h of admission were matched with another patient with the same diagnosis and propensity score who had not been catheterized. The results showed an increased mortality (odds ratio 1.24) in the patients receiving right heart catheterization.

The study was widely debated and received the expected barrage of criticism associated with any publication that challenges the accepted wisdom. Concerns were expressed in the UK that the study was not relevant to the UK ICU

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patient population, as patients with lung cancer and metastatic colon cancer are not often treated on UK ICUs. However, 80% of patients studied by Connors and colleagues had acute respiratory failure or MSOF, the bread and butter of UK ICU practice. More importantly, an analysis of the Scottish Intensive Care Society database gave a similar result to the Connors study.[9] Concerns were also expressed about the validity of the case matching—whether the patients were truly matched or whether there was an unrecorded factor that was influencing both the physicians' decision to place a right heart catheter and the patient's chance of survival. This is a methodological limitation of case-matching studies and can never be adequately answered with this study design. The only solution is to perform another study using the best available design to remove confounding factors, which is the RCT.

There is obviously not a consensus view on the benefit of right heart catheterization in intensive care in the UK. The correspondence in the *British Medical Journal* that followed publication of the Connors' paper,[10–12] revealed a spread of opinion which is reflected in the wide range of right heart catheter use between units, varying from 3 to 76% of admissions in a recent survey of 69 UK ICUs conducted by the Intensive Care National Audit and Research centre (ICNARC). However, intensive care clinicians in the UK are clearly united in their view that answering the question is important, ranking evaluation of right heart catheterization amongst the three most important research priorities in a recent study.[13] Over 80% of Scottish intensive care clinicians surveyed indicated that they would welcome a clinical trial.[14] The NHS Research and Development Health Technology Assessment (NHS R&D HTA) Programme have responded to the speciality's concern by funding the first randomized controlled trial of the use of right heart catheterization in intensive care in the UK, the 'PAC-Man' study (Pulmonary Artery Catheters in patient Management).

This trial presents a unique set of challenges. Unlike most trials, the intervention under investigation is already in widespread use rather than being introduced with the trial. Thus, in participating units half the trial patients will be randomized not to receive a monitoring/treatment package that they would have otherwise received. The only way this can be ethically justified is if the clinicians involved have *equipoise*; that is, they believe that on current evidence it is impossible to determine if use of the right heart catheter increases, decreases or does not alter risk of mortality for intensive care patients. This is the only rational interpretation that can be placed on the available published data, but it will require courage, clear thinking and intellectual honesty to apply this to individual patients.

What is to happen to patients who refuse consent or whose relatives refuse assent for the study? A physician with true equipoise could take the view that there is no evidence for harm or benefit from the catheter, and could remove it from use for the duration of the trial, so the 'best available treatment' offered to patients outside the trial did not include right heart catheterization. Ethically this is perfectly acceptable as no physician has a duty to provide a therapy of unproven efficacy to any patient. Alternatively, patients who refuse consent or whose relatives refuse assent could all receive a right heart catheter on the basis that even in the absence of objective evidence of benefit, it comprises standard treatment in many units and so is the 'best available treatment'. Ethically, this is again an acceptable view, but it requires investigators to be disciplined and even-handed when recruiting for the trial and to present the arguments clearly, otherwise the natural tendency for relatives to favour the most active treatment will make them refuse assent, leading to poor recruitment and bias.

Clinical trials fall broadly into two categories: efficacy trials and effectiveness trials. *Efficacy* trials address whether an intervention can produce the desired effect in ideal circumstances. In the context of right heart catheters this translates to a study where the patient group studied, the indications for the catheter, the technique for placement and all subsequent management are rigorously controlled by protocol. This is the approach the American intensive care community has taken with the ARDSNet (http://hedwig.mgh.harvard.edu/ardsnet/ards05.html) study of right heart catheters in acute lung injury. The limitation of this approach is that the results are really only applicable to the patient group studied and the protocol used. In the UK, the NHS R&D HTA who are supporting the PAC-Man study have agreed to fund a pragmatic or *effectiveness* approach, where the use or otherwise of the catheter is determined by randomization but little more is controlled. The advantage with this type of trial is that the results can be immediately used to inform changes in the healthcare process to the advantage of a large number of patients. The disadvantage is that potential benefits to small well-defined subgroups of patients are masked and the number of patients required is larger. Both approaches are vulnerable to the naysayers, who would claim that either design did not address the particular group of patients they treat.

For the PAC-Man study to work as an effectiveness trial, all patients suitable for right heart catheterization on an ICU will have to be entered into the trial. The idea that some patients are too ill to be denied the 'benefits' of right heart catheterization immediately introduces a major bias in the study, removing the very patients likely to show a benefit. This problem has already stopped one randomized controlled trial of right heart catheterization undertaken in 1991 in Canada, where only 33 of 148 (22%) of eligible patients entering the ICUs were recruited.[15] The physicians involved thought it was 'unethical' not to catheterize the rest. They clearly did not have equipoise. We hope that with passage of time and more informed debate will ensure that the same situation does not occur in the UK.

The PAC-Man study is a unique opportunity for the UK intensive care community. Years of work by individuals and professional bodies have raised the profile of the specialty to the point where we have been entrusted with a large portion of the NHS R&D HTA budget to run a major study that will involve 6000 patients and a third of UK ICUs. The study will answer a question that no one in the worldwide ICU community has been able to address properly for 30 years. It is perhaps unfortunate that we could not make the first major, non-commercial, multi-centre clinical trial in UK ICUs a study of a new and exciting therapy, but the questions about right heart catheterization are important both to individuals and for the credibility of the specialty. The study will set up the infrastructure for many more trials and, with the involvement of such a large proportion of the UK intensive care community, allow important questions to be efficiently and quickly addressed.

Participation in the PAC-Man study will require intensive care physicians to take a clear and objective assessment of the evidence on which they base one of the cornerstones of their practice, and suspend their prejudices for a year whilst the study provides the definitive answer. The rewards to the speciality for this intellectual courage are enormous. The penalty for nihilism may be the attentions of the National Institute for Clinical Excellence (NICE), which came into existence on All Fools Day 1999, exactly half a century after Hellems' paper was submitted.

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Editorial II

Codeine phosphate in children: time for re-evaluation?

Codeine is a well-established drug in the pain armamentarium. It is classed as a 'weak opioid' and used to treat pain of mild to moderate severity, either alone or in conjunction with non-opioids. Its route of administration is usually oral or intramuscular (i.m.), although there is a growing interest in using the rectal route in children, from where it is rapidly absorbed, achieving a peak plasma concentration in 30–60 min.[1] In this recent study, a dose of codeine 1 mg kg^{-1} given either rectally or i.m. in children over 3 months old produced a peak codeine level at 30 min, but with a consistently lower plasma level when given rectally. The lower plasma level after rectal administration reflects the reduced bioavailability of the drug when given by the rectal route.[2]

Codeine or methylmorphine is an opium alkaloid about one-tenth as potent as morphine.[2] Its use is advocated in the management of acute and chronic pain. It is cited extensively in World Health Organisation (WHO) literature, being part of the WHO essential drugs list, for the management of pain from cancer and AIDS.[3] It is commonly used to manage pain after adenotonsillectomy,[4] dental extraction[5] and neurosurgery[1 6] in adults and children.

In the 1990s, the advent of Acute Pain Services brought a more organized management of pain in children.[7] As part of this phenomenon there has been a change in practice from using mainly morphine and paracetamol for pain control, to

Table 1 Paracetamol/codeine preparations. Optimal doses for children and infants over 3 months old. Oral dose paracetamol=20 mg kg^{-1} every 6 h. Oral dose codeine=1–1.5 mg kg^{-1} every 4–6 h

	Codeine dose (mg)	Paracetamol dose (mg)
Co-codamol 8/500	8	500
Co-codamol 30/500	30	500
Co-codamol 60/1000	60	1000

coordinated use of drug combinations which include non-steroidal anti-inflammatory drugs (NSAIDs) and codeine.[8] In the last 10 yr we have progressed from giving minimal analgesia, especially to infants and neonates, to widespread use of morphine for pain after major surgery in all ages of children. As respiratory depression remains the anaesthetist's greatest fear after morphine in very young children, codeine has been used in infants and neonates after major surgery.[9] Doses of codeine ranging from 0.5 to 1.5 mg kg^{-1} have been used to provide analgesia, with the smaller dosage being used in the younger patients.

In this issue, Williams and colleagues[10] review the evidence concerning codeine's analgesic efficacy and call it into question. Some studies have shown codeine to have a variable effect.[11 12] Codeine has been extensively used to provide analgesia following craniotomy, but a series of articles by Stoneham and Walters[13–15] demonstrate inadequate analgesia with codeine in adults and recommend the use of patient controlled analgesia (PCA) with morphine as a better alternative.

Following absorption, codeine undergoes extensive metabolism, with 5–15% undergoing O-demethylation with CYP2D6, a cytochrome P450 enzyme, to form morphine. It has been put forward that it is only this portion of the drug which produces analgesia,[16] although some believe that codeine has a small inherent analgesic action. The variable effect of codeine is a result of genetic polymorphism.[17] The cytochrome P450s are a multigene family of enzymes. The level of expression or function of these enzymes has a major effect on drug efficacy. Patients in whom the cytochrome P450 gene encoding contains inactivating mutations are 'poor metabolizers' (PMs), and have a severely compromised ability to metabolise drugs such as codeine, warfarin and amitriptyline among others. Pharmacogenetic testing is currently used in only a limited number of specialist centres around the world. We are still a long way from having a pharmacogenetic DNA chip for use at the bedside or in clinic to determine a patient's drug sensitivity.

So is it time to re-evaluate our use of codeine? Is there enough evidence for us to throw it in the bin? Drug research in children always lags significantly behind that in adults. Many pharmaceutical companies do not pursue a product license for their drugs to be used in children, because of cost. Codeine has a license to be used for pain control or as a cough suppressant in children over 1 yr old, given by the oral or i.m. route. It is not licensed for use rectally.[18] Despite codeine being an 'old' drug, there are few clinical studies in children which relate blood levels of codeine or morphine to pain score.[1] When pharmacokinetic studies are done, they rarely involve all paediatric age groups—from neonate to adolescent. We often depend on data from older patients to guide us in our dosing strategies. Is there any evidence in adults that codeine can provide good analgesia?

The last 10 yr has seen the use of systematic review to evaluate different analgesic drugs.[18] Combined data from multiple randomized controlled trials can be used to estimate the effectiveness of a drug or intervention with more validity than any single trial permits. A statistical concept, which is useful in measuring effectiveness is the number needed to treat (NNT) to produce a specified outcome. For an ideal analgesic this would be 1. The Oxford League Table of Analgesic Efficacy[19] ranks drugs in order of NNT to produce 50% pain relief for 4–6 h in patients with moderate to severe pain. Codeine 60 mg has a NNT of 17, and comes at the bottom of the table. Paracetamol 1000 mg has a NNT of 4.6 and paracetamol 1000 mg with codeine 60 mg a NNT of 1.9, illustrating the additive effect of combining the two drugs. The only drugs which score higher are the NSAIDs, particularly ibuprofen and diclofenac. Only ibuprofen is licensed for use in children to treat acute pain.

Just as in adults, NSAIDs can be contraindicated in children because of renal dysfunction, bleeding or gastro-intestinal upset. Sometimes we need a drug to manage a moderate degree of pain other than paracetamol. Some would say that we should use morphine—this may be like taking a hammer to crack a nut for some situations. Maybe before discarding codeine as a poor analgesic we should utilize the information gleaned from systematic reviews and use codeine in combination with paracetamol for managing moderate pain. The commercially available combined preparations may not always fit the bill when giving drugs on a weight basis (Table 1). Only Co-codamol 8/500 is licensed for use in children. Combined preparations remain non-user friendly for children; the low dose preparation contains too little codeine and the others are difficult to subdivide to give adequate doses of both drugs to all sizes of children. However, even without a suitable combined preparation for use in children, there is no reason why these drugs cannot be given in tandem to optimize their effectiveness.

In the meantime, drug research in children needs to be much more structured. Drugs need to be systematically assessed for effectiveness in all age ranges, from premature infants to adolescents, even drugs that have been available for many years. There is a general disapproval of giving drugs by the i.m. route to children and the rectal route is an increasingly attractive alternative especially in younger children. We need to know more about the pharmacokinetics of drugs depending on the route of administration and the effects that age and organ maturity have on drug behaviour. Pain assessment is difficult in preverbal children, but it is possible to perform with time and effort.[7] We need more studies which relate pain score to therapeutic blood levels of drugs in children. It may still be a little early to throw out codeine, particularly when we have few drugs adequately investigated with which to replace it.

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CLINICAL INVESTIGATIONS

Dose-dependent prophylactic effect of nicorandil, an ATP-sensitive potassium channel opener, on intra-operative myocardial ischaemia in patients undergoing major abdominal surgery

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Nicorandil, a nicotinamide nitrate derivative, relaxes vascular smooth muscle and reduces cardiac muscle contractility by increasing membrane potassium conductance, probably by activating ATP-sensitive potassium channels. In this prospective, randomized, double-blind, placebo-controlled clinical study, we examined the dose-dependent prophylactic effect of nicorandil on intra-operative myocardial ischaemia in 248 patients who had pre-operative risk factors for ischaemic heart disease and were undergoing major abdominal surgery. Patients in group HD (n=81) received a bolus dose of nicorandil 0.08 mg kg^{-1} and a continuous infusion of 0.08 mg kg^{-1} h^{-1}. Patients in group LD (n=87) received nicorandil 0.04 mg kg^{-1} and 0.04 mg kg^{-1} h^{-1}. Patients in the placebo (P) group (n=80) received the same volumes of saline. The patients were monitored with a three-lead clinical ECG monitor with an ST trending device from arrival in the operating theatre to the end of anaesthesia. Intra-operative myocardial ischaemia occurred significantly less frequently in the HD group (one patient, 1.2%) than in the LD (11 patients, 12.6%) and P groups (21 patients, 26.3%) (P<0.01), and in group LD significantly less than in group P (P<0.05). Administration of nicorandil had little effect on the patients' heart rate or arterial pressure. Three patients in group P and none in either treatment group developed myocardial infarction after surgery.

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Nicorandil, a nicotinamide nitrate derivative, relaxes vascular smooth muscle and reduces cardiac muscle contractility by increasing membrane potassium conductance, probably by activating adenosine triphosphate (ATP)-sensitive potassium channels.[1] Its pharmacological effects include reductions in myocardial preload and afterload. Nicorandil is an antianginal agent that is effective for treating various types of angina pectoris[2] and has been reported to be cardioprotective in several animal models of ischaemia–reperfusion injury and myocardial infarction.[3] Saito and colleagues[4] recently reported that, in humans, the intravenous administration of nicorandil reduced ischaemic changes in the intracoronary electrocardiograph (ECG) during percutaneous transluminal coronary angioplasty, without significant changes in systemic arterial pressure or coronary blood flow. Thus, nicorandil may have a direct cardioprotective action on the ischaemic myocardium at a clinically relevant dose. Imagawa and colleagues[5] have reported that nicorandil acts to protect the heart by the same mechanism as ischaemic preconditioning, namely, the opening of ATP-sensitive potassium channels.

Cardiovascular disease, especially ischaemic heart disease, continues to be a significant cause of perioperative morbidity and mortality. Mangano and colleagues[6 7] have reported that in non-cardiac surgical patients with, or at risk of, ischaemic heart disease, ischaemia is most frequent and most severe during the post-operative period and post-operative ischaemia appears to be associated with adverse cardiac outcome. However, Varma and colleagues[8] have reported that intra-operative ST-segment changes are associated with a higher incidence of perioperative myocardial

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infarction and adverse cardiac outcome. Knorring[9] has also reported that skilful anaesthesia is needed in patients at high risk of ischaemic heart disease undergoing non-cardiac surgery.

In this prospective, randomized, double-blind, placebo-controlled clinical study, we examined the dose-dependent prophylactic effect of nicorandil on intra-operative myocardial ischaemia and post-operative myocardial infarction in patients with pre-operative risk factors for ischaemic heart disease undergoing major abdominal surgery. The effect of nicorandil on arterial pressure and heart rate during anaesthesia was also studied.

Patients and methods

The study was performed at Tokyo Metropolitan Fuchu Hospital, Tokyo, Japan, between January 1998 and December 1999. With institutional approval and written, informed consent, we studied 262 patients aged >40 yr who had at least two pre-operative risk factors for ischaemic heart disease among 1386 patients undergoing major abdominal surgery. Pre-operative risk factors for ischaemic heart disease were as described by Mangano and colleagues,[6] Fleisher and Barash[10] and Ishiguro and colleagues,[11] namely hypertension, diabetes mellitus, hyperlipidemia, current smoker, age >70 yr, obesity, family history of ischaemic heart disease, or peripheral vascular disease. Patients with the following conditions were excluded because ECG monitoring would be unreliable: digoxin therapy, left bundle branch block, left ventricular hypertrophy and strain changes in the lateral chest leads on the pre-operative 12-lead ECG. Patients receiving anti-angina drugs, such as nitrates, calcium antagonists and β-blockers, for ischaemic heart disease or hypertension were also excluded because these drugs would affect perioperative myocardial ischaemia.[12 13]

All patients were premedicated with ranitidine 150 mg taken orally 90 min before the induction of anaesthesia and with atropine 0.01 mg kg^{-1} and hydroxyzine 1 mg kg^{-1} injected i.m. 30 min before the induction of anaesthesia. Patients on antihypertensive medication continued to take these drugs until the morning of their surgery.

Before arriving in the operating theatre, 248 patients were assigned randomly to one of three groups. Patients in group HD (n=81) received an intravenous bolus dose of nicorandil 0.08 mg kg^{-1} after application of routine monitoring, followed by a continuous infusion of nicorandil 0.08 mg kg^{-1} h^{-1}. Patients in group LD (n=87) received an intravenous bolus dose of nicorandil 0.04 mg kg^{-1} and a continuous infusion of 0.04 mg kg^{-1} h^{-1}. Patients in the placebo group, group P (n=80), received the same volumes of saline. All physicians and nursing staff caring for the patients perioperatively were blinded to these groups.

A pulse oximeter was attached and a 20-gauge radial arterial catheter placed to monitor arterial pressure; patients were then monitored continuously with a three-lead clinical ECG monitor with an ST trending device (BSM-8502; Nihon Kohden, Tokyo, Japan) until the end of anaesthesia. This is a microprocessor-based solid state system programmed with algorithms for accurate analysis of both ischaemia and arrhythmia. The ST measurement point on the ST trending monitor was taken as the mean of three ST-segment points, namely the J point + 40–44 ms, + 44–48 ms and + 48–52 ms. Leads II and V5 were monitored for ST segment changes. An ischaemic episode was defined as a reversible ST segment shift from the baseline of ⩾0.1 mV depression or ⩾0.2 mV elevation lasting for ⩾1 min. All recorded ischaemic episodes of ST-segment changes were verified visually by one of the investigators blinded to assignment of the groups.

A standardized intra-operative anaesthetic technique was used. After a thoracic epidural catheter had been inserted, general anaesthesia was induced with propofol 2 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation. Before surgery began, buprenorphine 2 μg kg^{-1} was injected via the epidural catheter. Anaesthesia was maintained with 33–50% inspired oxygen, 50–67% nitrous oxide and 0.5–1.0% sevoflurane; a continuous infusion of 1% mepivacaine (0.1 ml kg^{-1} h^{-1}) was injected via the epidural catheter. All patients were managed so as to maintain mean arterial pressure within 20% of pre-operative values and heart rate between 50 and 90 beats min^{-1}. If the systolic arterial pressure dropped below 90 mm Hg, 5 mg ephedrine was given; if this had no effect, a continuous infusion of dopamine was started at 3 μg kg^{-1} min^{-1} up to a maximum of 10 μg kg^{-1} min^{-1}. If the heart rate dropped below 50 beats min^{-1}, 0.5 mg atropine was given. Acetated Ringer's solution was infused at 7–10 ml kg^{-1} h^{-1}. After completion of surgery, neuromuscular blockade was reversed with 2 mg neostigmine and 1 mg atropine and the patient's trachea was extubated.

Both 12-lead ECG and serum creatine kinase MB isoenzyme CK-MB concentrations were obtained from all patients daily for the first 3 days after surgery. A diagnosis of a post-operative myocardial infarction required the following triad: clinical suspicion of myocardial infarction, change in the post-operative 12-lead ECG and documented increase in serum CK-MB concentrations (>50 IU litre^{-1}).

The plasma concentration of nicorandil was measured in another 14 patients receiving the high-dose (n=7) or low-dose regimen (n=7). Blood samples (5 ml) were taken from radial arterial catheters 5, 20, 60 and 120 min after administration of nicorandil. Plasma concentrations were analysed using the HPLC system (Mitsubishi BCL, Tokyo, Japan).

Table 1 Physical and clinical characteristics of the patients and intra-operative data. Data are mean (SD) or number of patients. IHD=ischaemic heart disease; RPP=rate–pressure product (systolic arterial pressure×heart rate); MAP=mean arterial pressure

	Group		
	P (n=80)	LD (n=87)	HD (n=81)
Patient characteristics			
Age, yr (range)	65 (12) (40–93)	69 (10) (40–87)	67 (11) (40–91)
Gender: male/female	46/34	50/37	41/40
Height, cm	159 (8)	158 (8)	159 (9)
Weight, kg	58 (11)	57 (10)	59 (12)
Body surface area, m^2	1.6 (0.1)	1.6 (0.2)	1.6 (0.2)
Risk factors for IHD			
Hypertension	41	48	47
Diabetes mellitus	26	29	29
No. treated with glibenclamide	6	5	5
Hyperlipidaemia	12	10	5
Current smoker	47	47	37
Age >70 yr	32	44	45
Obesity	23	23	24
Family history of IHD	4	2	6
Peripheral vascular disease	5	11	11
Intra-operative drugs			
Sevoflurane (ml)	46 (18)	45 (14)	41 (16)
Mepivacaine (mg kg^{-1})	4 (1)	4 (1)	4 (1)
Dopamine use	24	28	25
Ephedrine use	29	32	30
Atropine use	2	2	2
Intra-operative data			
Duration of anaesthesia (min)	240 (100)	263 (113)	239 (120)
Duration of surgery (min)	179 (98)	203 (109)	180 (109)
Maximum RPP (mm Hg min^{-1})	13 240 (2986)	13 460 (3293)	12 440 (3446)
Minimum MAP (mm Hg)	57 (8)	55 (8)	59 (8)
Blood loss (g)	511 (553)	621 (774)	527 (693)

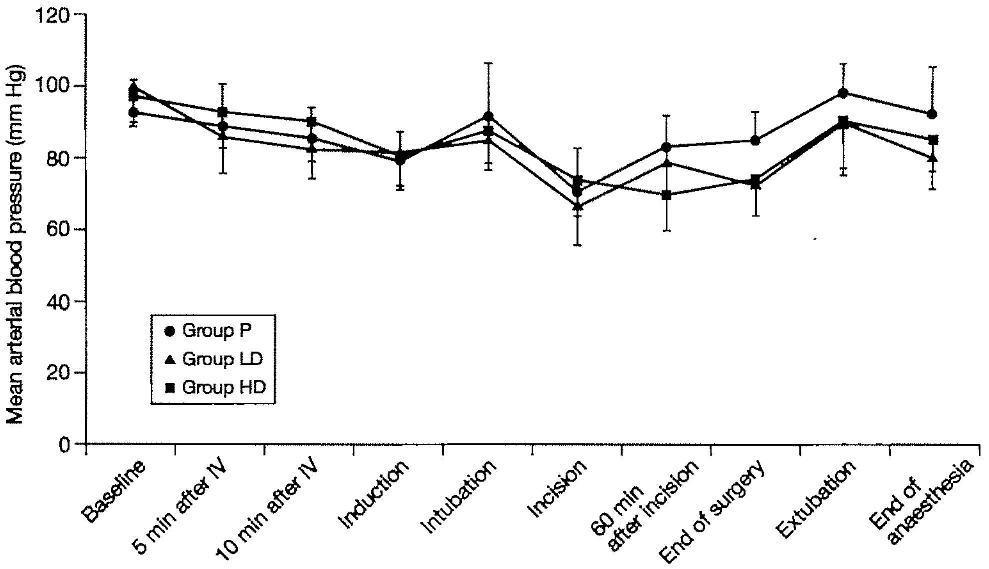

Fig 1 Mean arterial blood pressure after administration of nicorandil. Data are mean±SD. There was no significant difference among the groups.

Continuous parametric variables were analysed using one-way analysis of variance. Nonparametric variables were compared with Pearson's χ^2 test, Fisher's exact test and the Kruskal–Wallis test. Repeated-measures analysis of variance was used for the analysis of mean arterial blood pressure and heart rate after administration of nicorandil. A P value of <0.05 was considered statistically significant; P values are reported only when significance was found. Results are expressed as the mean (SD) unless otherwise indicated.

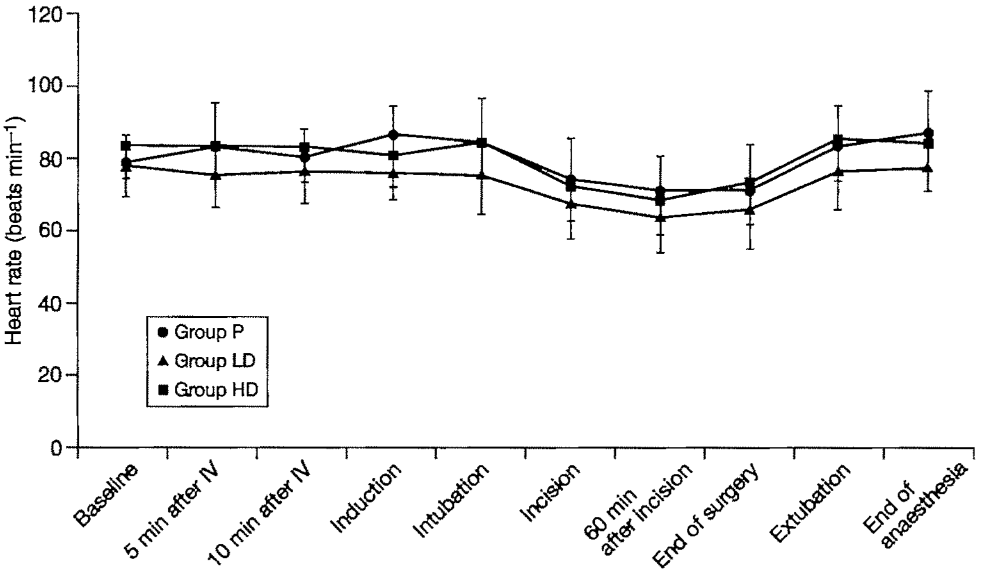

Fig 2 Heart rate after administration of nicorandil. Data are mean± SD. There was no significant difference among the groups.

Table 2 Changes in plasma nicorandil concentration after a bolus and continuous infusion. Data are mean (SD) (ng ml^{-1}). Group LD received a bolus of 0.04 mg kg^{-1} and an infusion of 0.04 mg kg^{-1} h^{-1}; group HD received a bolus of 0.08 mg kg^{-1} and an infusion of 0.08 mg kg^{-1} h^{-1}

Group	Plasma nicorandil concentration (ng ml^{-1})			
	after 5 min	after 20 min	after 60 min	after 120 min
LD	106 (21)	71 (17)	81 (20)	87 (31)
HD	221 (64)	166 (70)	183 (46)	232 (86)

Results

The physical and clinical characteristics of the patients and intra-operative data are summarized in Table 1. The use of anaesthetic and inotropic drugs was similar between the groups. The mean arterial pressure and heart rate after administration of nicorandil are shown in Figures 1 and 2, respectively. There was no significant difference among the groups.

Intra-operative myocardial ischaemia occurred significantly less frequently in group HD (one patient, 1.2%) than in groups LD (11 patients, 12.6%) and P (21 patients, 26.3%) ($P<0.01$), and in group LD significantly less than in group P ($P<0.05$). Severe transient hypotension and ventricular arrhythmia occurred in two of 11 patients in group LD and in five of 21 patients in group P. There was no post-operative myocardial infarction in groups HD and LD, but three patients in group P had non-fatal post-operative myocardial infarction, one patient each on days 0, 1 and 2 after surgery. All three patients had intra-operative ischaemic episodes with severe transient hypotension and ventricular arrhythmia.

The plasma concentrations of nicorandil measured in 14 patients are shown in Table 2.

Discussion

Mangano and colleagues[6] have reported that 27% of patients with, or at risk of, ischaemic heart disease undergoing non-cardiac surgery exhibited intra-operative ECG ischaemic episodes. Of these, 77% occurred without acute change in blood pressures and 4% were associated with post-operative myocardial infarction. Our data for group P are remarkably similar. Intra-operative myocardial ischaemia occurred significantly less frequently in group HD than in groups LD and P and in group LD significantly less than in group P, demonstrating the dose-dependent prophylactic effect of nicorandil on intra-operative myocardial ischaemia in patients with pre-operative risk factors for ischaemic heart disease undergoing major abdominal surgery. Although current thinking puts more emphasis on post-operative ischaemia and myocardial damage than on intra-operative ischaemia,[6 7] all three of our patients who sustained a post-operative infarct had intra-operative ischaemia and hypotension. Further studies are required to assess the possible effect of nicorandil in prevention of post-operative myocardial infarction.

Administration of nicorandil by a bolus and continuous infusion had little influence on the patients' heart rate or arterial pressure in our study. Ito and colleagues[14] have reported that no side-effects occurred with a bolus dose of nicorandil 4 mg kg^{-1} followed by a continuous infusion of nicorandil 6 mg h^{-1} in patients with an anterior acute myocardial infarction. Uchino and colleagues[15] have reported that the effective plasma concentration of nicorandil that had no adverse cardiovascular effects was 40–300 ng ml^{-1}. The plasma concentration of nicorandil in our study was 70–230 ng ml^{-1}.

Takaoka and colleagues[16] have suggested that nicorandil directly protects the myocardium against ischaemic injury via ATP-sensitive potassium channels. The mechanism by which nicorandil has a direct cardioprotective action on the ischaemic myocardium is thought to be the same as the mechanism of ischaemic preconditioning.[5] Ischaemic preconditioning is a phenomenon described in 1986 by Murry and colleagues[17] as brief periods of ischaemia that render the myocardium resistant to a subsequent longer period of ischaemia. This endogenous protective mechanism has been shown to occur in many species.[18 19] On the other hand, Dodds and colleagues[20] have reported that prophylactic infusion of nitroglycerine, one of the organic nitrates, during non-cardiac surgery does not reduce intra-operative myocardial ischaemia. Therefore, the effects of nicorandil in our study may have been mediated via ATP-sensitive potassium channels rather than by its nitrate.

Our study has several potential limitations. First, we defined an ischaemic episode using the ST trending monitor (leads II and V5). Many studies have demonstrated the superiority of two-dimensional trans-oesophageal echocardiography over ECG for the intra-operative detection of myocardial ischaemia,[21] and ST trending monitors have an overall sensitivity and specificity of 74% and 73% relative to two-lead Holter ECG.[22] Sole reliance on ST trending monitors for the detection of myocardial ischaemia may be insufficient, although we obtained hard copies of ECG strips for visual confirmation of potential wave-form changes.

Second, patients with diabetes mellitus receiving oral sulfonylurea hypoglycaemic agents, such as glibenclamide, were included in our study. Glibenclamide antagonizes ATP-sensitive potassium channels[18 19] and blocks ischaemic preconditioning in the intact rat heart[18] and human myocardium.[19] Nakae and colleagues[23] have reported that glibenclamide does not antagonize the change in coronary blood flow caused by nicorandil, but its effect on the myocardial protective potential of nicorandil is not known. However, in our study a similar number of diabetic patients were treated with glibencamide in each group (Table 1) and pretreatment with glibencamide did not seem to obscure the protective effect of nicorandil.

Other possible drawbacks of our study are the ischaemic preconditioning-like effect of sevoflurane and the influence of thoracic epidural anaesthesia. Novalija and colleagues[24] have reported that preconditioning with sevoflurane, like ischaemic preconditioning, improves not only postischaemic contractility, but also basal flow, bradykinin- and nitroprusside-induced increases in flow and effluent NO concentration in isolated pig hearts; the protective effects of both sevoflurane preconditioning and ischaemic preconditioning are reversed by ATP-sensitive potassium channel antagonism. However, these effects are unlikely to occur at the concentrations of sevoflurane used in our study.[24 25] There is evidence that thoracic epidural anaesthesia (T1–5) has an effect on myocardial ischaemia through cardiac sympathetic blockade which increases the luminal diameter of stenotic epicardial coronary arteries and reduces myocardial oxygen demand.[26] As all patients in our study received thoracic epidural anaesthesia, the effects of nicorandil observed were in addition to any effect of the epidural.

In conclusion, nicorandil reduced the incidence of intra-operative myocardial ischaemia without affecting heart rate or arterial pressure. We demonstrated the dose-dependent prophylactic effect of nicorandil, an ATP-sensitive potassium channel opener, on intra-operative myocardial ischaemia in patients with pre-operative risk factors for ischaemic heart disease undergoing major abdominal surgery.

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Prediction of volatile anaesthetic solubility in blood and priming fluids for extracorporeal circulation

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Volatile anaesthetics are often used during cardiopulmonary bypass (CPB). To understand the kinetics of inhaled anaesthetics during CPB, anaesthetists should understand changes in blood solubility caused by fluid use. We set out to predict the solubility of three volatile anaesthetics, desflurane, isoflurane and halothane, during CPB by determining: (i) their solubility in fresh whole blood and eight CPB priming fluids at 37°C; (ii) the effect of temperature on the solubility of these anaesthetics in lactated Ringer's, gelofusin, banked blood and plasma; (iii) their solubility in different mixtures of these four priming fluids at different temperatures; and (iv) their estimated and actual solubility in blood during hypothermic CPB. We calculated solubility using a concept of volume fraction partition coefficient and compared estimated and measured solubilities. For the three anaesthetics tested, solubilities are in the order: fresh whole blood ≈ plasma > banked blood > normal saline ≈ lactated Ringer's ≈ gelofusin ≈ Haemaccel ≈ hydroxyethyl starch > mannitol. The solubilities of the anaesthetics in all priming fluids increased logarithmically at lower temperatures ($P<0.05$). The volume-fraction estimates of the partition coefficients were within approximately ±20% of the measured values for all values of solubility. The corresponding estimates of solubility for CPB blood samples were between −36% and +24% of the measured values. During normothermic CPB, blood solubility of volatile anaesthetics would be unchanged when using plasma, slightly reduced when using banked blood and markedly reduced when using crystalloids and colloids.

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During cardiopulmonary bypass (CPB), volatile anaesthetics can be added to the oxygenator to provide anaesthesia,[1 2] regulate systemic vascular resistance[3 4] and reduce hormonal responses to CPB.[5 6] The rate of wash-in and wash-out of volatile anaesthetics via oxygenators depends on their solubility in blood.[7] Two important factors affect the solubility of volatile anaesthetics: hypothermia increases solubility,[7–12] but crystalloid haemodilution decreases it.[11 12] Although the effect of hypothermia on solubilities in saline and plasma has been studied,[12] and although the effects of hypothermia and crystalloid haemodilution on blood solubility of halothane, enflurane and isoflurane have been observed in CPB,[13–16] the solubility of volatile anaesthetics in colloid and other priming fluids has not been investigated. Data for the recently introduced agent, desflurane, are limited. To provide such information for predicting blood/gas partition coefficients ($\lambda_{B/G}$) during CPB, we studied the following: (i) solubility of desflurane, isoflurane and halothane in eight CPB priming fluids; (ii) effect of temperature on the solubility of these anaesthetics in four CPB priming fluids; (iii) estimated and measured solubilities of the three anaesthetics in different combinations of the four priming fluids at different temperatures; and (iv) predicted and measured $\lambda_{B/G}$ of the three agents during hypothermic CPB.

Methods

Liquid/gas partition coefficients (λ) were measured using a two-stage headspace equilibration method (see below) for fresh whole blood, plasma, banked blood, CPB priming fluids, mixtures of different primes, and diluted blood in

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Table 1 Composition of mixtures of priming fluids

	Amount (ml) in mixture			
Mixture	**Lactated Ringer's**	**Gelofusin**	**Plasma**	**Banked blood**
1	54	108	0	108
2	54	54	108	54
3	102	68	68	34
4	68	34	34	136
5	216	0	0	54
6	39	193	39	0
7	45	45	90	90
8	45	135	90	0
9	193	0	77	0
10	39	154	77	0

CPB. Coefficients were obtained for desflurane, isoflurane and halothane simultaneously by using a mixture of the three anaesthetic vapours in air.

Solubility of volatile anaesthetics in eight CPB priming fluids

The solubilities of desflurane, isoflurane and halothane in banked blood (Blood Bank, Beijing, China), plasma (Blood Bank, Beijing), normal saline (China Dazhong, Tianjing, China), lactated Ringer's solution (China Dazhong, Tianjing, China), gelofusin (Braun, Switzerland), Haemaccel (Behring, Germany), hydroxyethyl starch (Changshu Pharmaceutical, Jiangshu, China) and mannitol (ZhenDa TianQing, Jiangshu, China) were measured by gas chromatography (see below). We used 10 samples of each solution at 37°C. To compare fresh whole blood with banked blood, the solubility in fresh whole blood (Fuwai Hospital, Beijing, China) and ACD solution (Fuwai Hospital) was measured. Collection of fresh whole blood was approved by the Committee of Scientific Research in Fuwai Hospital and informed consent was obtained from each of the 10 male healthy volunteers aged 23 (22–25) yr (mean (range)).

Effect of temperature on solubility of anaesthetics in CPB priming fluids

The solubility of desflurane, isoflurane and halothane in lactated Ringer's solution (a crystalloid solution), gelofusin (a colloid solution), plasma and banked blood was measured at 37, 33, 29, 25, 21 and 17°C. We used six samples of each fluid at each temperature.

Solubility of anaesthetics in mixtures of different priming fluids

Lactated Ringer's solution, gelofusin, plasma and banked blood were mixed in different proportions, as determined by a computer, to give 494 mixtures, each with a volume of approximately 270 ml. We randomly chose 10 of these mixtures which had different proportions of the four constituents (Table 1). The solubilities of desflurane, isoflurane and halothane in these 10 mixtures were measured at 37, 33, 29, 25, 21 and 17°C, using six samples from each mixture at each temperature. Estimated λ of the mixtures was calculated from the equation: estimated $\lambda=\Sigma(\lambda_x \times F_x)$ where λ_x is the solubility of the agent in each constituent x and F_x is the fractional concentration of each constituent in the total mixture. We called this the volume fraction partition coefficient.

Solubility of anaesthetics in blood during CPB

After approval from the Committee of Scientific Research in Fuwai Hospital, we obtained informed consent from 20 adult patients undergoing valve replacement surgery requiring CPB. Patients were anaesthetized using total intravenous anaesthesia. Lactated Ringer's solution or gelofusin was administered before CPB. The CPB circuit were primed with lactated Ringer's solution and gelofusin. Blood samples were taken 15 min after the beginning of CPB to allow a steady state to be reached after haemodilution by priming fluid. Urine output, type and volume of infused fluids, and CPB priming fluid were noted. Blood loss was estimated before the blood sample was collected. The solubility of desflurane, isoflurane and halothane in each blood sample (measured $\lambda_{B/G}$ of diluted blood in CPB) were measured at 37, 33, 29, 25, 21 and 17°C. The solubilities of the three anaesthetics in each blood sample were estimated using the concept of volume fraction partition coefficient. The method is given in the Appendix.

Gas chromatography and determination of solubility

Anaesthetic concentration was measured with a GOW-MAC 580 gas chromatograph equipped with a 6 m stainless steel column (0.32 cm internal diameter) packed with Chromosorb-P60/80 mesh maintained at 75°C. We used a 10 ml min^{-1} nitrogen carrier flow, and a flame ionization detector supplied with hydrogen at 35 ml min^{-1} and air at 300 ml min^{-1}. The output was passed to a TAI-SSC922 integrator and peak areas were calculated. Under these conditions, the peaks of desflurane, isoflurane and halothane were completely separated. Primary and secondary (compressed gas tank) standards were used for calibration. Primary standards were made by injecting an aliquot of each anaesthetic into a glass flask of known volume with a syringe. Because of the high saturated vapour pressure of desflurane, we took steps to ensure that no desflurane was lost. Liquid desflurane and the syringe were kept at 4°C in a refrigerator. Liquid desflurane was drawn into the cool syringe at 4°C in the refrigerator and was injected into the flask or tank immediately. The primary standards (glass flask) were used to calibrate the secondary standards; the secondary standards (tank) were injected at intervals to calibrate the gas chromatograph during each study. All R^2 of the linear regression between concentration of anaesthetics and peak area of gas chromatography output were higher than 0.9995 throughout the study. The regression equation was used to convert peak area to agent concentration. Peak areas were proportional to concentrations over the entire range of the concentrations tested.

A gas mixture of desflurane, isoflurane and halothane for equilibration in solubility determination was prepared as follows. A stainless steel cylinder (8.1 litres) was evacuated to a pressure of about 0.5 atm less than ambient. Liquid desflurane, isoflurane and halothane were aspirated into the cylinder and the cylinder was filled with compressed air. We calculated the volume of the three liquid anaesthetics transferred into the cylinder and the compressed air pressure required in the cylinder to ensure that the total pressure of each anaesthetic in the cylinder was <90% of its saturated vapour pressure. The cylinder was rolled for 30 min to mix the contents in the cylinder thoroughly. The anaesthetic concentrations in the cylinder were then calibrated using the primary standard; it contained 1.65% desflurane, 1.78% isoflurane and 1.85% halothane.

A 20 ml gas-tight glass syringe, calibrated precisely and capped with a three-way stopcock, was sealed by coating the plunger with a thin layer of silicone grease. The gas-tightness of these grease-sealed syringes was tested before the study: the concentrations of anaesthetic vapours in the syringes decreased by no more than 2% over 8 h. This also showed that the grease did not absorb anaesthetic. Approximately 7 ml of liquid sample was drawn into a syringe and the above-mentioned anaesthetic gas mixture was added to give 18 ml; the three-way stopcock was then closed. The syringe was shaken vigorously and immersed in a waterbath at the chosen test temperature. Every 15 min for 2 h, the syringe was shaken vigorously for 5–10 s. After the third shaking, the plunger of the syringe was withdrawn to the 20 ml position with the stopcock closed, causing a small negative pressure in the syringe. The stopcock was then opened briefly to allow air into the syringe and to restore ambient pressure in the syringe. After this 2 h period (the first equilibration period), the concentration of anaesthetic (C_1) in the gas phase of the syringe was analysed by gas chromatography. All the gas and some of the liquid in the syringe were expelled and exactly 4 ml of liquid sample (V_L) was retained in the syringe for the second equilibration. Vapour-free air was drawn in to move the plunger to the 18 ml position. The syringe was shaken vigorously and immersed in the waterbath with the same temperature as in the first equilibration period. The second equilibration had the same sequence of shaking, volume adjustment and timing as in the first equilibration. At the end of the second equilibration period, the concentrations of anaesthetics in gas phase (C_2) were analysed by gas chromatography.

The total amount of anaesthetic (ml, in liquid plus gas phase) after the second equilibration is equal to that in the liquid phase which was retained in syringe after the first equilibration. This relationship can be expressed as:

$$C_2 \times V_G + C_{L2} \times V_L = C_{L1} \times V_L \tag{1}$$

where V_G and V_L are the gas volume and sample volume retained in the syringe for the second equilibration, respectively; C_{L1} and C_{L2} are the anaesthetic concentrations in liquid samples at the end of the first and second equilibration, respectively. λ is defined as the ratio of anaesthetic concentration (vol%) in liquid phase to that in gas phase (vol%), e.g. $C_{L1}=\lambda \times C_1$ and $C_{L2}=\lambda \times C_2$. Substituting these into equation (1) yields:

$$C_2 \times V_G + \lambda \times C_2 \times V_L = \lambda \times C_1 \times V_L \tag{2}$$

This equation can be rearranged to give:

$$\lambda = (V_G/V_L) \times (C_2/(C_1 - C_2)) \tag{3}$$

Equation (3) was used to calculate λ.

Statistical analysis

Means and standard deviations were obtained for λ in priming fluids and blood. Solubilities in each priming fluid at 37°C for each anaesthetic were compared with those in fresh whole blood using Student's *t*-test. The ratio of mean solubility in each priming fluid and mean solubility in fresh whole blood ($R_{P/B}$) was calculated. Repeated-measures analysis of variance was used to determine the difference among the three anaesthetics for each priming fluid. We related $\log_e\lambda$ in each fluid to temperature, and calculated residual standard deviation (RSD) and 95% confidence limits (CL) of the slope and intercept of the regression lines. To assess the concept of volume fraction partition coefficient and the methods of predicting solubility given in the Appendix, regression and Bland and Altman's 'limits of agreement' analysis[17] were performed between estimated λ in mixtures of priming fluids and in CPB blood and the corresponding measured λ. $P<0.05$ was accepted as statistically significant.

Results

Table 2 shows the solubility of desflurane, isoflurane and halothane measured at 37°C. Their solubilities in fresh whole blood were not significantly different from those in plasma ($P>0.05$), but were significantly greater than those in the other priming fluids and in ACD solution ($P<0.05$).

For all three anaesthetics, the liquid/gas partition coefficients increased as temperature decreased (Table 3; four CPB priming fluids in step (ii), diluted blood during CPB in step (iv)). To estimate λ in CPB blood in step (iv), we used λ values from our previous study.[18] The solubilities were in the order: desflurane < isoflurane < halothane in all conditions. As temperature decreased, $\log_e\lambda$ increased linearly ($P<0.05$). The temperature coefficient of λ (percentage change in λ per degree centigrade) was calculated.[19]

Details of the fitted linear equations for the dependence of $\log_e\lambda$ on temperature are given in Table 4. The RSDs are in terms of $\log_e\lambda$ and lie between 0.021 and 0.075 for different

Table 2 Solubility of desflurane, isoflurane and halothane in eight priming fluids, fresh whole blood and ACD solution at 37°C (n=10). Data are shown as mean (SD) [95% CL]. $R_{P/B}$ is the ratio of mean solubility in each priming fluid to mean solubility in fresh whole blood for a given anaesthetic

Priming fluid	Desflurane		Isoflurane		Halothane	
	λ	$R_{P/B}$	λ	$R_{P/B}$	λ	$R_{P/B}$
Fresh whole blood	0.522 (0.056) [0.482–0.562]		1.343 (0.117) [1.259–1.427]		2.435 (0.245) [2.260–2.610]	
Plasma	0.525 (0.043) [0.494–0.555]	1.006	1.350 (0.121) [1.264–1.436]	1.005	2.215 (0.208) [2.066–2.363]	0.910
Banked blood	0.454 (0.028) [0.434–0.475]	0.870	1.169 (0.101) [1.097–1.241]	0.870	2.141 (0.151) [2.033–2.249]	0.879
Normal saline	0.282 (0.011) [0.274–2.290]	0.540	0.529 (0.019) [0.515–0.542]	0.394	0.755 (0.027) [0.736–0.775]	0.301
Lactated Ringer's	0.279 (0.008) [0.273–0.284]	0.534	0.532 (0.015) [0.521–0.543]	0.396	0.757 (0.025) [0.739–0.774]	0.311
Gelofusine	0.280 (0.011) [0.272–0.288]	0.536	0.564 (0.023) [0.547–0.580]	0.420	0.776 (0.022) [0.760–0.792]	0.319
Haemaccel	0.284 (0.010) [0.277–0.292]	0.544	0.562 (0.016) [0.550–0.573]	0.418	0.783 (0.021) [0.768–0.798]	0.322
Hydroxyethyl starch	0.279 (0.011) [0.271–0.286]	0.534	0.545 (0.020) [0.531–0.560]	0.406	0.769 (0.027) [0.750–0.788]	0.316
Mannitol	0.218 (0.009) [0.212–0.225]	0.418	0.442 (0.017) [0.429–0.454]	0.329	0.654 (0.024) [0.637–0.671]	0.269
ACD solution	0.293 (0.004) [0.289–0.296]	0.561	0.557 (0.010) [0.550–0.563]	0.415	0.779 (0.023) [0.753–0.785]	0.320

Table 3 Solubility of anaesthetics in four fluids, fresh whole blood (from previous study[18]) and CPB blood at different temperatures. Data are shown as mean (SD). Temp. coef.=temperature coefficient (%/°C), i.e. the slope of regression line of $\log_e\lambda$ on temperature in °C[19]

Solutions	Number of samples	Temp. coef. (%/°C)	Temperature (°C)					
			37	33	29	25	21	17
Desflurane								
Lactated Ringer's	6	–4.16	0.283 (0.005)	0.314 (0.003)	0.343 (0.005)	0.438 (0.024)	0.532 (0.035)	0.629 (0.064)
Gelofusin	6	–3.09	0.303 (0.005)	0.346 (0.013)	0.393 (0.007)	0.463 (0.005)	0.522 (0.011)	0.545 (0.033)
Banked blood	6	–2.78	0.459 (0.036)	0.529 (0.055)	0.581 (0.015)	0.646 (0.038)	0.754 (0.026)	0.792 (0.035)
Plasma	6	–2.75	0.484 (0.007)	0.547 (0.014)	0.602 (0.011)	0.744 (0.019)	0.780 (0.015)	0.809 (0.015)
Fresh whole blood	6	–2.83	0.550 (0.019)	0.626 (0.021)	0.684 (0.038)	0.724 (0.030)	0.800 (0.044)	1.036 (0.092)
Diluted blood in CPB	20	–4.20	0.379 (0.045)	0.413 (0.040)	0.499 (0.047)	0.587 (0.042)	0.697 (0.077)	0.867 (0.102)
Isoflurane								
Lactated Ringer's	6	–4.81	0.541 (0.015)	0.599 (0.012)	0.696 (0.033)	0.888 (0.066)	1.142 (0.112)	1.345 (0.121)
Gelofusin	6	–3.94	0.550 (0.027)	0.676 (0.030)	0.762 (0.009)	0.926 (0.015)	1.080 (0.033)	1.203 (0.078)
Banked blood	6	–3.75	1.118 (0.105)	1.334 (0.206)	1.539 (0.070)	1.811 (0.119)	2.120 (0.135)	2.347 (0.149)
Plasma	6	–3.96	1.166 (0.034)	1.369 (0.026)	1.412 (0.041)	1.943 (0.067)	2.324 (0.089)	2.416 (0.113)
Fresh whole blood	6	–3.74	1.377 (0.050)	1.610 (0.164)	1.832 (0.135)	2.088 (0.208)	2.568 (0.282)	2.888 (0.231)
Diluted blood in CPB	20	–4.66	0.967 (0.137)	1.071 (0.140)	1.306 (0.111)	1.548 (0.206)	1.875 (0.327)	2.461 (0.324)
Halothane								
Lactated Ringer's	6	–4.73	0.742 (0.026)	0.845 (0.027)	0.993 (0.048)	1.283 (0.106)	1.545 (0.088)	1.843 (0.143)
Gelofusin	6	–3.97	0.792 (0.033)	0.945 (0.051)	1.051 (0.058)	1.302 (0.026)	1.540 (0.046)	1.719 (0.117)
Banked blood	6	–4.25	1.812 (0.221)	1.981 (0.323)	2.342 (0.177)	3.050 (0.136)	3.598 (0.335)	3.954 (0.385)
Plasma	6	–4.49	1.900 (0.056)	2.204 (0.061)	2.311 (0.063)	3.084 (0.116)	3.914 (0.126)	4.461 (0.246)
Fresh whole blood	6	–4.33	2.588 (0.119)	3.115 (0.370)	3.593 (0.315)	4.175 (0.436)	5.238 (0.421)	6.175 (0.490)
Diluted blood in CPB	20	–4.92	1.730 (0.265)	1.850 (0.268)	2.399 (0.388)	2.800 (0.534)	3.365 (0.738)	4.641 (0.796)

media at different temperatures; these correspond to RSDs of between 2.1% and 7.5% of the arithmetic values of λ.

As anticipated, $\log_e\lambda$ of desflurane, isoflurane and halothane in the prime mixtures increased linearly as temperature decreased. We found a direct linear relationship between logarithm of estimated λ ($\log_e\lambda_e$) and measured λ ($\log_e\lambda_m$) in mixed primes for desflurane, isoflurane and halothane (P<0.05, Figure 1A). Figure 1B shows the 'limits of agreement' analysis between estimated and measured $\log_e\lambda$. The mean difference between estimated and measured $\log_e\lambda$ was –0.010 and the SD was 0.105, which indicated that the estimated λ in the mixtures of primes were within +22% and –20% of the measured values of λ.

A direct linear relationship was found between the logarithm of estimated λ ($\log_e\lambda_e$, calculated according to Appendix) and measured λ ($\log_e\lambda_m$) in CPB blood (P<0.05, Figure 2A). Figure 2B shows the 'limits of agreement' analysis between estimated and measured $\log_e\lambda$. The mean difference between estimated and measured $\log_e\lambda$ was –0.115 and the SD was 0.164, which indicated that the estimated λ in the CPB blood were within +24% and –36% of the measured values of λ.

Discussion

Although volatile anaesthetics are regularly used for open heart surgery, the solubility of anaesthetics in different CPB priming fluids has not been described before. Partition coefficients in all primes at 37°C were smallest with desflurane and greatest with halothane, a similar pattern as in fresh whole blood. This suggests that the differences in pharmacokinetics between the

Table 4 Regression equations for predicting solubility from temperature (°C) for four priming fluids, fresh whole blood (from previous study[18]) and CPB blood. $\mathrm{Log}_e\lambda = \mathrm{slope} \times T(°\mathrm{C}) + \mathrm{intercept}$. RSD=residual standard deviation; R^2=coefficient of determination for regression line; CL=confidence limit

	Slope (95% CL)	Intercept (95% CL)	RSD	R^2
Desflurane				
Lactated Ringer's	–0.042 (–0.050, –0.033)	–0.221 (–0.026, 0.467)	0.0532	0.976
Gelofusin	–0.031 (–0.037, –0.025)	–0.034 (–0.198, 0.130)	0.0354	0.982
Banked blood	–0.028 (–0.032, –0.024)	0.266 (0.151, 0.382)	0.0250	0.988
Plasma	–0.027 (–0.036, –0.019)	0.309 (0.070, 0.549)	0.0519	0.951
Fresh whole blood	–0.028 (–0.038, –0.018)	0.437 (0.160, 0.714)	0.0600	0.940
Diluted blood in CPB	–0.042 (–0.048, –0.036)	0.536 (0.366, 0.706)	0.0368	0.990
Isoflurane				
Lactated Ringer's	–0.048 (–0.057, –0.039)	1.102 (0.853, 1.352)	0.0540	0.982
Gelofusin	–0.039 (–0.044, –0.035)	0.883 (0.753, 1.013)	0.0282	0.992
Banked blood	–0.038 (–0.041, –0.034)	1.518 (1.419, 1.618)	0.0215	0.996
Plasma	–0.040 (–0.052, –0.027)	1.604 (1.257, 1.951)	0.0752	0.951
Fresh whole blood	–0.037 (–0.041, –0.034)	1.700 (1.600, 1.800)	0.0217	0.996
Diluted blood in CPB	–0.047 (–0.055, –0.039)	1.636 (1.412, 1.859)	0.0484	0.984
Halothane				
Lactated Ringer's	–0.047 (–0.053, –0.041)	1.413 (1.252, 1.574)	0.0348	0.992
Gelofusin	–0.040 (–0.044, –0.035)	1.237 (1.109, 1.366)	0.0278	0.994
Banked blood	–0.043 (–0.051, –0.034)	2.132 (1.894, 2.370)	0.0516	0.980
Plasma	–0.045 (–0.056, –0.034)	2.254 (1.938, 2.569)	0.0684	0.968
Fresh whole blood	–0.043 (–0.047, –0.039)	2.547 (2.439, 2.655)	0.0234	0.996
Diluted blood in CPB	–0.049 (–0.060, –0.038)	2.297 (1.987, 2.607)	0.0671	0.974

three anaesthetics will not be affected during CPB. However, when a priming fluid is mixed with blood, the solubility in blood will decrease to an extent which depends on $R_{P/B}$ (Table 2); the smaller the ratio, the greater the reduction in λ for the mixture. For all the three anaesthetics tested, $R_{P/B}$ of the eight priming fluids are in the following order: plasma (~1.00) > banked blood > normal saline ≈ lactated Ringer's solution ≈ gelofusine ≈ Haemaccel ≈ hydroxyethyl starch ≈ ACD solution > mannitol (Table 2). This order implies that, during normothermic infusion and normothermic CPB, λ in diluted blood would be unchanged by using plasma, slightly decreased by using banked blood and greatly decreased by using crystalloid and colloid solutions.

As anticipated, reduction in temperature caused an increase in solubility of the anaesthetics in all priming fluids, mixtures and CPB blood. This is consistent with the change for fresh whole blood.[7–12 18] Table 3 gives the temperature coefficients of λ. Taking all agents and all solutions tested in this study into account, no correlation was found between temperature coefficient and its λ at 37°C. However, for a given solution (with a minor exception for lactated Ringer's), the magnitudes of the temperature coefficients were in the same order as the partition coefficients at 37°C: desflurane < isoflurane < halothane.

We assumed that the solubility of an anaesthetic in a mixture of different solutions is equal to the sum of the solubility in each component multiplied by its volume fraction, a concept we call 'volume fraction partition coefficient'. This concept was substantiated in this study. For example, 1 unit of banked blood (250 ml in volume) used in this study consists of 200 ml (80% in volume fraction) whole blood and 50 ml (20% in volume fraction) ACD solution, and solubility of desflurane in banked blood at 37°C would be (0.52×80%)+(0.29×20%). The estimated solubilities of desflurane, isoflurane and halothane in banked blood were 0.47, 1.18 and 2.10, respectively, almost identical to the measured solubilities of banked blood (0.45, 1.17 and 2.14, respectively; Table 2). We also estimated solubility in 10 mixtures containing different proportions of priming fluids and found a close relationship between measured and estimated solubility (Figure 1A). The limits of agreement (equal to mean±2 SD of the differences, which will include about 95% of the data points) are 0.201 and –0.221 (Figure 1B). We have shown that the solubility of volatile anaesthetics in CPB primes can be predicted and that the concept of volume fraction partition coefficient is useful for the prediction.

For the agents studied, wash-in and wash-out will be quickest for desflurane and slowest for halothane at any given temperature, and slower at low temperature for all agents (Table 3), but quicker on dilution of blood with priming fluids (other than plasma) (Table 2). During CPB, hypothermia will increase anaesthetic blood solubility and haemodilution will reduce it. The effects of these two factors on blood solubility of halothane, enflurane and isoflurane have been observed in CPB.[13–16] It is not practical to monitor the solubility of the anaesthetics during CPB. If body temperature and the nature and degree of haemodilution by priming fluid are monitored, solubility can be estimated to within about –36% to 24% of the measured value (Figure 2). Therefore, changes in the rates of wash-in and wash-out of the anaesthetics are likely.

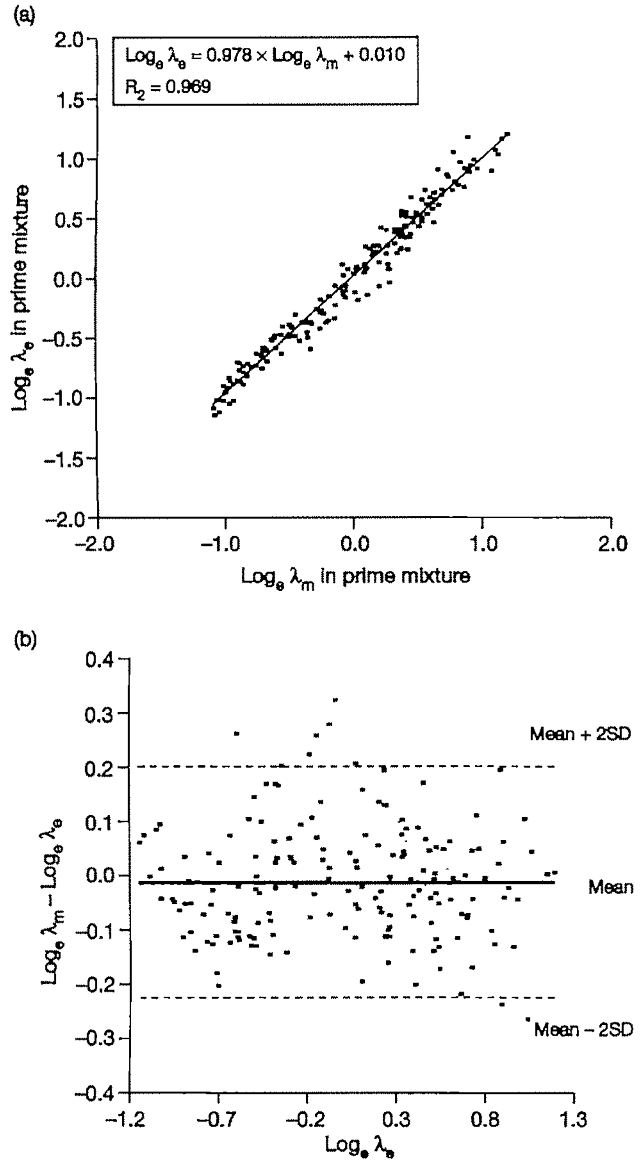

Fig 1 (A) Logarithm of estimated λ in prime mixtures ($\log_e\lambda_e$) plotted against logarithm of measured λ. There were 180 samples, representing the mean λ values of three anaesthetics in 10 mixtures of priming fluids at six temperatures. A direct linear relationship was found between $\log_e\lambda_e$ and $\log_e\lambda_m$ ($P<0.05$). (B) Differences between $\log_e\lambda_m$ and $\log_e\lambda_e$ in mixtures of priming fluids plotted against corresponding $\log_e\lambda_e$. The mean difference between $\log_e\lambda_m$ and $\log_e\lambda_e$ (-1.006×10^{-2}) and mean±2 SD (0.201 to −0.221) are shown.

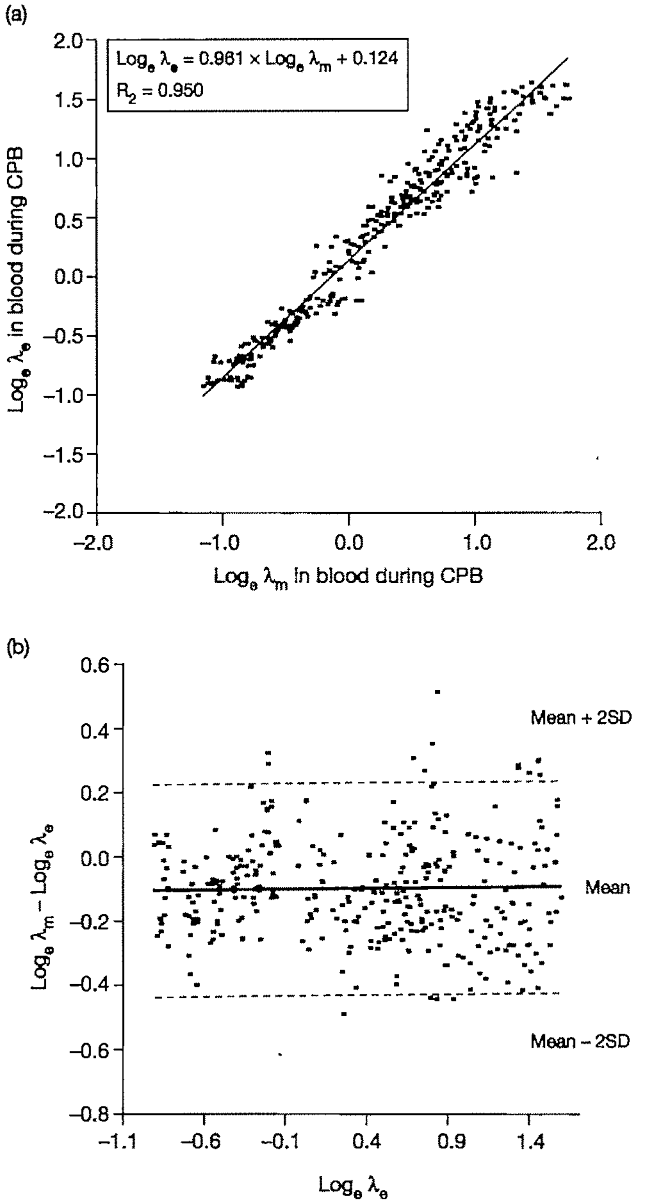

Fig 2 (A) Logarithm of estimated λ in CPB blood ($\log_e\lambda_e$) are plotted against logarithm of measured λ. There were 360 samples, representing the mean λ values of the three anaesthetics in 20 patients at six temperatures. A direct linear relationship was found between $\log_e\lambda_e$, and $\log_e\lambda_m$ ($P<0.05$). (B) Differences between $\log_e\lambda_m$ and $\log_e\lambda_e$ of CPB blood plotted against corresponding $\log_e\lambda_e$. The mean difference between $\log_e\lambda_m$ and $\log_e\lambda_e$ (−0.115) and mean±2 SD (0.214 to −0.444) are shown.

Our methods have some limitations. We cannot accurately estimate blood loss and circulating blood volume and did not take metabolism of colloid into account. This may have caused the systematically greater value of limits of agreement in predicting λ in CPB blood than that in prime mixtures (−36% to +24% in CPB blood compared with about ±20% in prime mixtures). However, our method will help anaesthetists judge changes in blood solubility of volatile anaesthetics during CPB, and the effect of this change on their pharmacokinetics.

Acknowledgements

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Appendix: estimating the solubility of volatile anaesthetics in CPB blood

(1)Estimate following circulating volumes (ml): (i) fresh whole blood volume (V_{fwb}), i.e. patient's body weight (kg) multiplied by 70 (ml kg^{-1}); (ii) net added crystalloid volume (V_{cry}), i.e. (infused crystalloid plus primed crystalloid minus urine output)/3; (iii) added colloid volume (V_{col}), i.e. infused colloid plus primed colloid; (iv) added banked blood volume (V_{bb}), i.e. infused banked blood plus primed banked blood; (v) added plasma volume (V_p), i.e. infused plasma plus primed plasma; and (vi) total circulating blood volume (V_{total}) = $V_{fwb}+V_{cry}+V_{col}+V_{bb}+V_p$.

(2) Calculate solubilities for fresh whole blood (λ_{fwb}), crystalloid (λ_{cry}), colloid (λ_{col}), banked blood (λ_{bb}) and plasma (λ_p) at the temperature at which λ is estimated by using the equations in Table 4.

(3) Estimated λ of CPB blood=$((V_{fwb}\times\lambda_{wb})+(V_{cry}\times\lambda_{cry})+(V_{col}\times\lambda_{col})+(V_{bb}\times\lambda_{bb})+(V_p\times\lambda_p))/V_{total}$

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British Journal of Anaesthesia **86** (3): 345–8 (2001)

Compound A production from sevoflurane is not less when KOH-free absorbent is used in a closed-circuit lung model system

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In an *in vitro* study, less compound A was formed when a KOH-free carbon dioxide absorbent was used. To confirm this observation we used a lung model in which carbon dioxide was fed in at 160 ml min^{-1} and sampling gas was taken out for analysis at 200 ml min^{-1}; ventilation aimed for a PE'_{CO_2} of 5.4 kPa. The soda lime canister temperatures in the inflow and outflow ports (T_{in} and T_{out}) were recorded. In six runs of 240 min each, a standard soda lime, Sodasorb (Grace, Epernon, France) was used and in eight runs KOH-free Sofnolime (Molecular Products, Thaxted, UK) was used. Liquid sevoflurane was injected using a syringe pump to obtain 2.1% E'. Compound A was measured by capillary gas chromatography combined with mass spectrometry. Median (range) compound A_{insp} increased to a maximum of 22.7 (7.9) ppm for Sodasorb and 33.1 (20) for Sofnolime at 60 min and decreased thereafter; the difference between groups was significant ($P<0.05$) at each time of analysis up to 240 min. The canister temperatures were similar in both groups and increased to ~40°C at 240 min. Contrary to expectation, compound A concentrations were greater with the KOH-free absorbent despite similar canister temperatures with both absorbents.

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Keywords: carbon dioxide, absorption, soda lime; model, lung

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During sevoflurane anaesthesia, particularly during low flow and closed-circuit procedures, compound A can be formed. This is the main breakdown product of the reaction of sevoflurane with the carbon dioxide absorbent used in the circuit. Compound A concentrations are greater when Baralyme is used as carbon dioxide absorbent than when soda lime is used.[1 2] However, soda lime varies according to the manufacturer. NaOH and KOH are mostly used as initiators in the carbon dioxide binding process. These highly reactive products could provoke the breakdown of sevoflurane in the canister in the breathing circuit. In experimental conditions less compound A was formed with a KOH-free soda lime.[3] We studied the *in vitro* behaviour of a KOH-free commercial soda lime (Sofnolime; Molecular Products, Thaxted, UK) using closed circuit conditions, to maximize the eventual production of compound A.

Experimental set-up

A test lung was used to obtain stable, identical concentrations of sevoflurane and carbon dioxide. To simulate clinical conditions, a continuous flow of 160 ml min^{-1} carbon dioxide was delivered through a needle in the bellows of the test lung. To simulate oxygen consumption, a continuous flow of 200 ml min^{-1} was taken out of the test lung at a T-piece at the outlet. This gas flow was fed to a gas analyser (Ultima; Datex, Helsinki, Finland) for assessing all respiratory gases and was scavenged, rather than being returned to the circuit. If 100% oxygen was used, oxygen consumption was simulated satisfactorily.

The Y-piece of a circle system was connected to the artificial lung. A modified PhysioFlex (Dräger, Lübeck, Germany) closed-circuit anaesthetic machine was used (Figure 1). The built-in fan (for circulating the breathing gases) was switched off and two classical unidirectional valves were placed in the breathing circuit. A respiratory frequency of 10 bpm and a tidal volume of 490 ml were used to obtain a PE'_{CO_2} of 5.4 kPa. In this system the 'consumed' oxygen or volume loss is replaced by an equal (vol/vol) inflow of oxygen, and displayed on the screen of the machine as oxygen consumption. The apparatus was cleaned carefully before each use to eliminate any contam-

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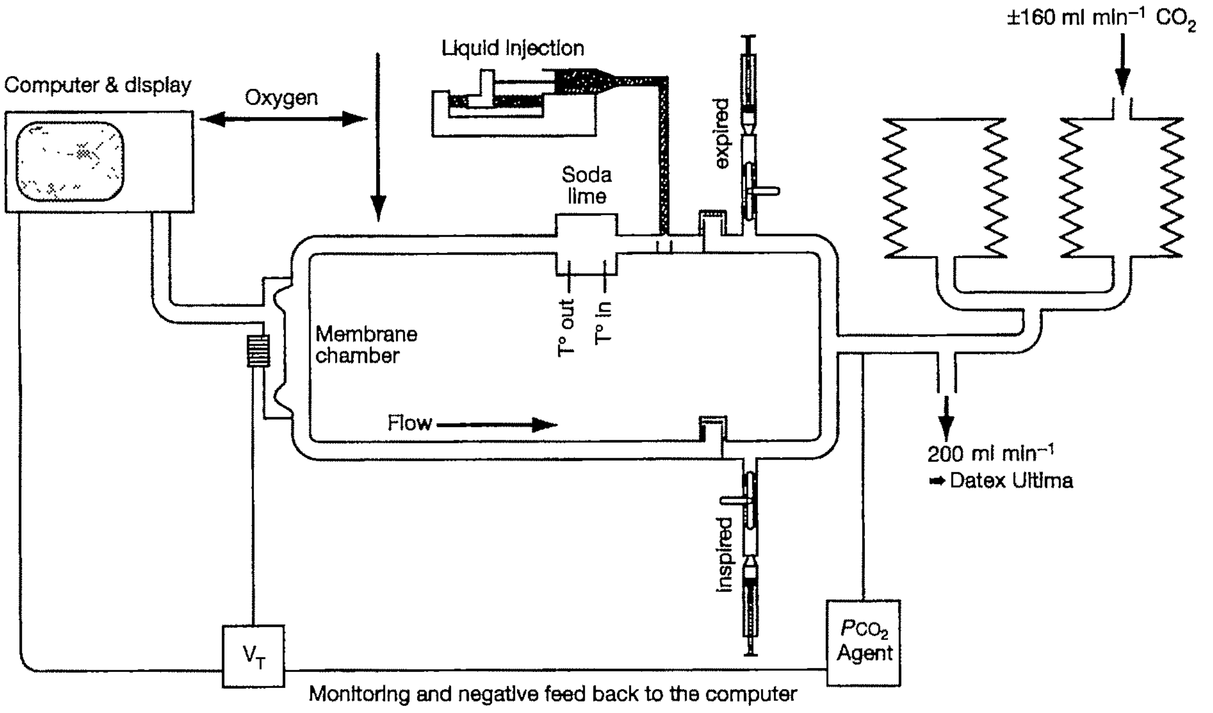

Fig 1 Schematic design of the modified PhysioFlex machine connected to the 'model lung'.

ination from a previous study and checked for complete air-tightness. At the start of the study the lowest possible setting of 0.2% sevoflurane had to be set to close the active charcoal canister, which would otherwise have absorbed compound A. After initial equilibration, liquid sevoflurane was given using a syringe pump (Graseby 3500; Watford, UK), injected in a small copper reservoir fitted to the breathing circuit. The aim was an end-tidal sevoflurane concentration of 2.1 vol%.

Two thermistors were placed in the 800 ml soda lime canister to measure the temperature. One was in the inflow port, measuring the inflow temperature (T_{in}) and the other in the outflow port (T_{out}). From the outflow the gases passed through an inner cylindrical pipe within the canister to the breathing circuit. Another thermistor was placed in the Y-piece of the breathing circuit to measure the temperature there (T_Y).

Eight runs with fresh Sofnolime and six runs with standard Sodasorb soda lime (Grace, Epernon, France) were carried out in random order. Fresh commercially available soda limes, stored under normal conditions, were used for each run. According to the available information, the Sofnolime contained 3% NaOH, >75% $Ca(OH)_2$ and 12–19% H_2O and the Sodasorb contained 2.68% NaOH, 3% KOH, 89% $Ca(OH)_2$ and 12–19% H_2O. Gas samples of 2 ml were taken in airtight syringes for the determination of compound A. The syringes were connected to the breathing circuit by three-way valves and Luer-lock connections, one situated in the inspiratory limb (for compound A_{insp}) and one in the expiratory limb (for compound A_{exp}). The gas samples were immediately transferred to sealed glass head-space vials.

Compound A was assayed by capillary gas chromatography combined with mass-spectrometric detection (HP 6890-5973 MSD). Injection was fully automated by a technique based on head-space sampling (1 ml). In order to place enough analyte mass on to the capillary columm, cryofocusing on Tenax sorbent (liquid nitrogen, −80°C) placed in the injector liner was used. A thick-film capillary column (CP-select 624, a 6% cyanopropylphenyl-dimethyl-silicone stationary phase) allowed adequate retention and excellent isothermal separation (38°C). Helium was used as carrier gas at a flow rate of 1 ml min^{-1}. The mass-spectrometer detector was operated in the full-scan mode. The mass spectrum (electron ionization mode) of compound A is characterized by prominent peaks at *m/z* 69, 128, 161 and 180, the last representing the molecular ion (M^+). The ion at *m/z* 128 was selected as the target ion for quantitative purposes. Before each analysis, a standard curve of eight points was prepared and injected. Standards of compound A in the gas phase were prepared, using liquid volumetric dilutions of stock solutions of compound A and sevoflurane in ethyl acetate. 1-Iodo-2,2,2-trifluoroethane was chosen as an internal standard. Good linearity over a range of 0.5–75 ppm (v/v) was obtained (average correlation coefficient 0.996 (*N*=10)). Within-day (*N*=6) and total (*N*=10) reproducibility were tested at three different concentrations (0.5, 10 and 75 ppm). The coefficients of variation ranged from 4.1 to 10.0%. The limit of detection (LOD), using a signal-to-noise ratio of 3, was 0.1 ppm, whilst the limit of quantification (LOQ) was 0.3 ppm, using a signal-to-noise criterion of 10 and still assayed with adequate reproducibility (CV%<15%).

At the end of the preparation of the apparatus, and 5, 15, 30, 60, 90, 120, 150, 180, 210 and 240 min after the start of sevoflurane administration, we recorded $P\text{E}'_{CO_2}$, sevoflurane E', T_{in}, T_{out}, compound A_{insp} and compound A_{exp}. The data were analysed using repeated measures Anova and/or Mann–Witney U-tests. A P value of <0.05 was considered statistically significant.

Results

The means for $P\text{E}'_{CO_2}$ (5.4–5.7 kPa) and for sevoflurane E' (2.1–2.2%) in both groups of carbon dioxides were similar and not significantly different over the entire measurement period. The inflow of oxygen (indicated on the PhysioFlex screen) was around 200 ml/min in both groups. The total amount (mean (SD)) of liquid sevoflurane injected into the circuit was also identical (Sodasorb group, 7.32 (0.35) ml; Sofnolime group, 7.26 (1.0) ml). The median and range of T_{in} and T_{out} are shown in Figures 2 and 3. No statistically significant difference was found between the Sodasorb and Sofnolime canister temperatures recorded at any time. The increase in T_{out} was significant (P<0.05) up to 30 min, but not significant after 30 min, in both the Sodasorb and Sofnolime groups. No difference was found for T_Y, which remained between 24 and 25.5°C throughout the study. The median and range of compound A_{insp} and compound A_{exp} are shown in Figures 4 and 5. Compound A_{insp} increased up to 60 min (median (range) 22.7 (7.9) ppm in Sodasorb and 33.1 (20.0) ppm in Sofnolime), after which it declined. A statistically significant difference (P<0.05) between Sodasorb and Sofnolime was found at each time for compound A_{insp} and compound A_{exp}, the values for Sofnolime always being greater.

Discussion

The presence of strong bases such as NaOH and KOH may be a factor in the dehalogenation of sevoflurane to compound A. Cunningham and co-workers[3] found that the correlation with compound A generation was stronger for KOH (expressed as percentage base) than for NaOH. They found the lowest concentration of compound A with 5% NaOH, and KOH-free Sofnolime was also associated with the lowest concentration of compound A, but these findings are controversial. Dry absorbent containing only $Ca(OH)_2$ produces less carbon monoxide with desflurane than any other lime, with KOH having a greater capacity to generate carbon monoxide than NaOH (4).

In the present study the inspired and expired concentrations of compound A increased sooner with the KOH-free Sofnolime than with the classical Sodasorb; the difference was always significant. However, the curves of these concentrations were similar with time. The peak was seen

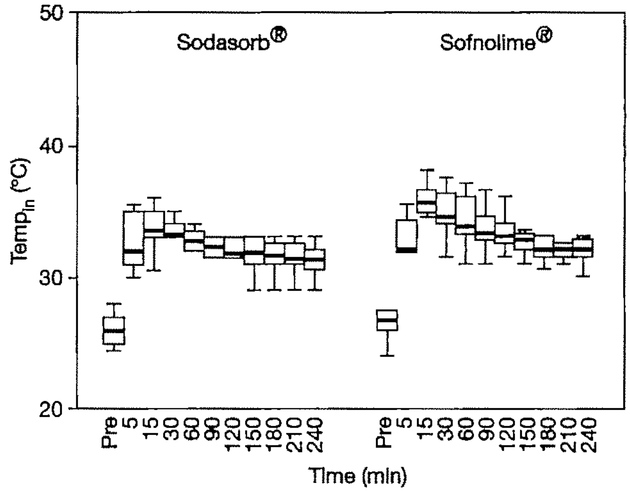

Fig 2 Median, interquartile values and range of canister T_{in} in Sodasorb and Sofnolime groups.

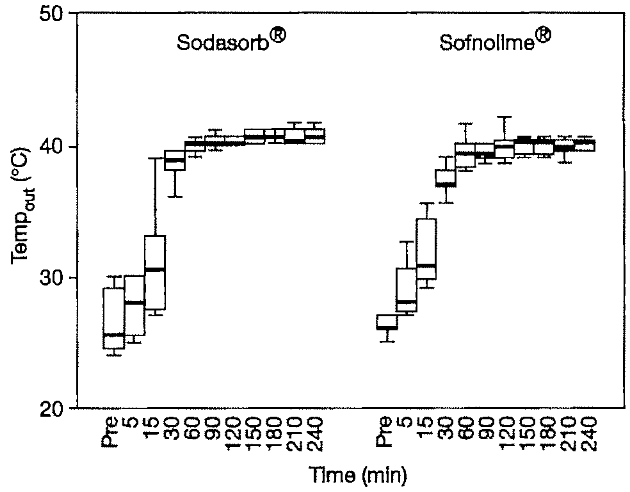

Fig 3 Median, interquartile values and range of canister T_{out} in Sodasorb and Sofnolime groups.

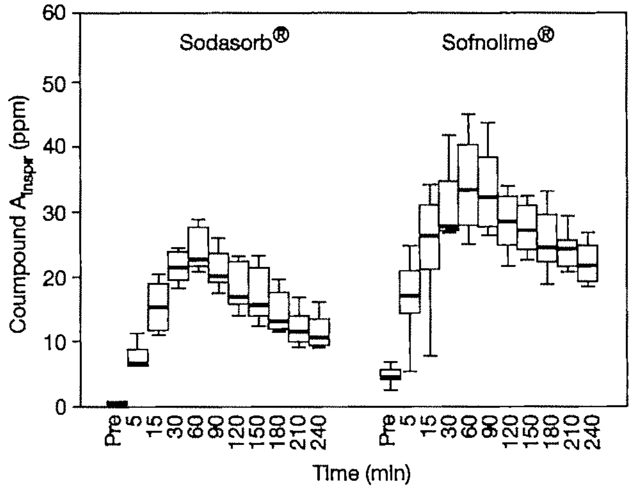

Fig 4 Median, interquartile values and range of compound A_{insp} in Sodasorb and Sofnolime groups: statistical significance at P<0.05 between the two groups at all assessment times.

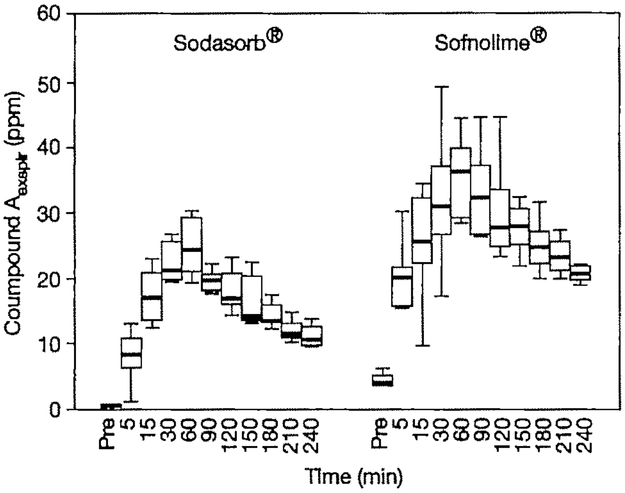

Fig 5 Median, interquartile values and range of compound A_{exp} in Sodasorb and Sofnolime groups: statistical significance at $P<0.05$ between the two groups at all assessment times.

at 60 min, with a mean compound A difference of 14 ppm between the two carbon dioxide absorbents; the one for Sofnolime was greater. Compound A values decreased slowly up to 240 min, as has also been reported in clinical studies.[5] In the early preparation of the circuit, when a very low sevoflurane concentration of 0.2% E′ had to be set, to close the activated charcoal canister, a much greater inspired concentration of compound A was found with Sofnolime than with Sodasorb (mean 4.5 and 0.6 ppm, respectively; $P<0.05$), suggesting that compound A is generated very rapidly with Sofnolime. The canister temperature T_{in} was initially greater than T_{out}, but from 30 min onwards T_{out} was greater than T_{in} and attained 40°C with both soda limes. No temperature difference was found at any time between either soda lime, showing that the higher compound A concentrations with Sofnolime could not have been generated by a greater canister temperature. This might have been assumed, knowing that a positive correlation has been found between soda lime temperature and compound A generation,[6 7] but other, as yet unknown factors must also be involved in the production of compound A. In experimental conditions with *dry* soda lime, less compound A was generated with Sofnolime than with normal soda lime.[8]

Our results contrast with those reported in recent clinical low-flow studies.[9 10] Higuchi and coworkers[10] found that less compound A was generated with KOH-free soda limes Drägersorb 800 Plus and Medisorb, which contain only 0.003% KOH, than with classical Drägersorb 800. The Sofnolime used in our study contained 3% NaOH, whereas Medisorb contained only 1% NaOH and Drägersorb 800 Plus 2% NaOH. The Sodasorb used in our study contained 2.68% NaOH, more than the 2% present in Drägersorb 800. These facts may explain the differences in their results and suggest the importance of the KOH and/or NaOH concentration in the carbon dioxide absorbent. The same considerations apply to the results of Yamakage and colleagues,[9] who compared Medisorb with the classical soda lime Wakolime, which contains 2.6% KOH and 1.3% NaOH. These authors report that Drägersorb 800 Plus has a KOH concentration of 3.0%, whereas Higuchi and colleagues[10] quote a concentration of 0.003%, making scientific comparison difficult.

We could not support the hypothesis that simply eliminating KOH from soda lime would reduce the formation of compound A. Indeed, we found even higher concentrations than with classical soda lime Sodasorb. Factors other than KOH, such as the concentration of NaOH, are even more important in the generation of compound A. Although our study is entirely experimental, it does simulate carbon dioxide production and oxygen consumption. Our results need to be confirmed in future clinical studies.

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Arterial to end-tidal carbon dioxide tension difference in children with congenital heart disease[†]

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In children with congenital cyanotic heart disease, right-to-left intracardiac shunting causes an obligatory difference between arterial and end-tidal carbon dioxide tension (Pa_{CO_2}–PE'_{CO_2}) as venous blood, rich in carbon dioxide, is added to the arterial circulation. This obligatory Pa_{CO_2}–PE'_{CO_2} difference, which can be predicted from knowledge of oxygen saturation, haemoglobin concentration and Pa_{CO_2}, increases as oxygen saturation decreases, most markedly when the haemoglobin concentration is high. A second possible cause of the Pa_{CO_2}–PE'_{CO_2} difference is the effect of pulmonary hypoperfusion caused by the shunt. We studied 60 children undergoing cardiac surgery and compared the predicted the Pa_{CO_2}–PE'_{CO_2} difference with measured values to investigate the extent to which additional factors influence the clinically observed Pa_{CO_2}–PE'_{CO_2}. In many children, observed values were much greater than predicted, which is compatible with some degree of pulmonary hypoperfusion. However, this was not felt to represent the complete picture in all patients. Another cause of ventilation–perfusion mismatch was suspected in those children who showed a considerable improvement in oxygen saturation during ventilation with an increased FI_{O_2}. We believe that pulmonary congestion caused by large left-to-right shunts may further increase the Pa_{CO_2}–PE'_{CO_2} difference.

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Keywords: carbon dioxide, elimination; heart, congenital defects; blood, haemoglobin

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In children with normal cardiorespiratory function, arterial carbon dioxide tension (Pa_{CO_2}) during anaesthesia approximates to end-tidal carbon dioxide tension (PE'_{CO_2}).[1 2] In cyanotic children, however, the right-to-left intracardiac shunt has important effects on gas exchange. The addition of venous blood, relatively poor in oxygen and rich in carbon dioxide, to the systemic ventricle of the heart causes not only a reduction in arterial oxygen saturation, but also elevation of arterial PCO_2 above pulmonary capillary, alveolar, and end-tidal PCO_2. This reduction in the efficiency of carbon dioxide elimination, an apparent alveolar deadspace, is a primary effect of right-to-left shunting. Right-to-left shunting also reduces pulmonary blood flow, potentially causing alveolar hypoperfusion. This secondary effect increases alveolar deadspace still further, and has an additive effect on the arterial–alveolar PCO_2 difference and thus the Pa_{CO_2}–PE'_{CO_2}.

The theoretical relationship between the Pa_{CO_2}–PE'_{CO_2} difference and the arterial saturation in patients with right-to-left shunting has been described by Fletcher.[3] As saturation falls, the Pa_{CO_2}–PE'_{CO_2} difference increases proportionately. The increase in the Pa_{CO_2}–PE'_{CO_2} difference with decreasing saturation is greatest when the haemoglobin concentration is high. This relationship was confirmed in children with pulse oximeter saturations of 60–100%.[3]

Thus, in the absence of pulmonary hypoperfusion, Pa_{CO_2} can be predicted accurately in cyanotic children with otherwise normal lung function from knowledge of the PE'_{CO_2}, haemoglobin concentration and saturation.[4] However, should significant pulmonary hypoperfusion exist, then the Pa_{CO_2}–PE'_{CO_2} difference will always be greater than its estimate from first principles. The difference increases as saturation decreases, unless there is a compen-

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[†]Presented at the meeting of the Anaesthetic Research Society, Liverpool, March 2000.

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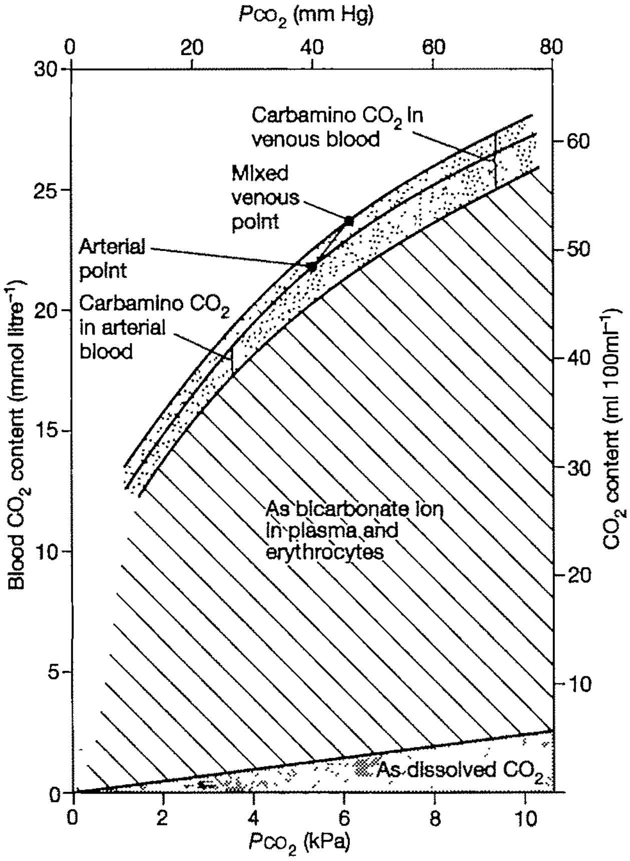

Fig 1 Components of the carbon dioxide dissociation curve for whole blood. Dissolved carbon dioxide and bicarbonate ion vary with P_{CO_2} but are little affected by the state of oxygenation of the haemoglobin. Carbamino carriage of carbon dioxide is strongly influenced by the state of oxygenation of haemoglobin but hardly at all by P_{CO_2}. (Reproduced with permission from *Nunn's Applied Respiratory Physiology*.[5])

satory increase in cardiac output, as may occur in severely hypoxaemic children.[4]

We investigated whether the effect of pulmonary hypoperfusion could be detected by comparing observed and predicted values for Pa_{CO_2}–$P\text{E}'_{CO_2}$ in children with congenital heart disease.

Theory

The theoretical relationship between the Pa_{CO_2}–$P\text{E}'_{CO_2}$ difference and saturation can be defined by the following equation:[3]

$$(Pa_{CO_2}-P\text{E}'_{CO_2})=\text{R}\times\text{Hb}\times0.0131\times(100-Sa_{O_2})/\text{k}$$

where R is the respiratory quotient, Hb is the haemoglobin concentration in grams per litre, 1.31 is the combining constant of haemoglobin in millilitres of oxygen per gram of haemoglobin, and k is the slope of the carbon dioxide dissociation curve for whole blood. It can be seen that Pa_{CO_2}–$P\text{E}'_{CO_2}$ will increase as saturation decreases and haemoglobin increases, reflecting the primary effect of the right-to-left shunt. This predicted difference takes no account of the effect of pulmonary hypoperfusion.

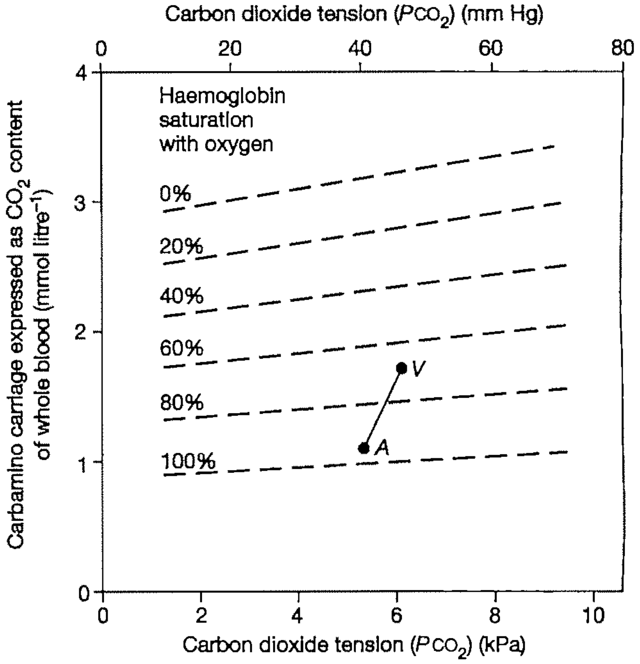

Fig 2 The broken lines on the graph indicate the carbamino carriage of carbon dioxide at different levels of saturation of haemoglobin with oxygen (Hb 15 g dl^{-1}). *A* represents arterial blood and *V* represents mixed venous blood in patients with no gas exchange lesion. (Reproduced with permission from *Nunn's Applied Respiratory Physiology*.[6])

Calculation of predicted (obligatory) Pa_{CO_2}–$P\text{E}'_{CO_2}$ difference in patients with intracardiac shunting

A. Calculate total arterial carbon dioxide content

(i) Using measured Pa_{CO_2}, determine bicarbonate carbon dioxide (ml litre^{-1}) from Fig. 1.

(ii) Using measured Pa_{CO_2}, Hb and saturation, determine carbamino carbon dioxide (ml litre^{-1}) from Fig. 2 (1 mmol litre^{-1}=22.4 ml litre^{-1}).

(iii) Add (i) to (ii) above to give total arterial carbon dioxide content.

B. Calculate pulmonary end-capillary carbamino content

Assume 100% saturation and standard carbamino content at haemoglobin concentration=15 g dl^{-1} of 22 ml litre^{-1} carbon dioxide. Correct for measured haemoglobin concentration.

C. Calculate arterial minus end-capillary oxygen difference

(i) End-capillary oxygen content=Hb×1.31+[((FI_{O_2}×(PB–$P\text{H}_2\text{O}$))–($P\text{E}'_{CO_2}$/R))×0.225] [using Hb in g litre^{-1}, $P\text{E}'_{CO_2}$ to estimate alveolar P_{CO_2} (kPa) and assuming standard values for barometric pressure (PB), $P\text{H}_2\text{O}$ and R (0.8)].

(ii) Arterial oxygen content=(Hb×1.31×Sa_{O_2}/100)+(Pa_{O_2}×0.225) (using Hb in g litre^{-1}, Pa_{O_2} in kPa).

(iii) Subtract (i) from (ii) above for arterial minus end-capillary oxygen difference (ml litre^{-1}).

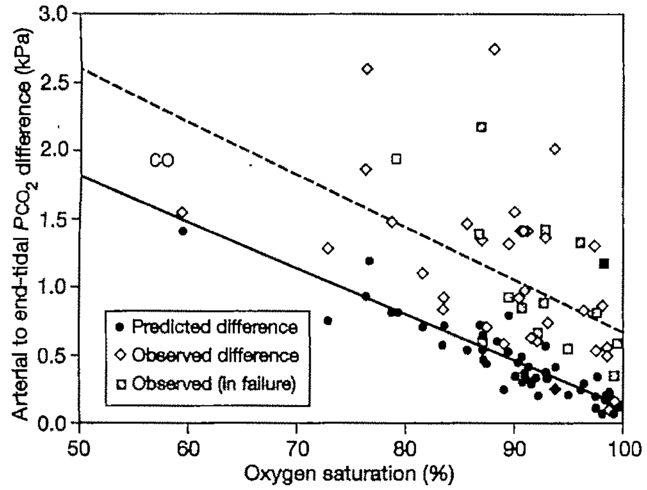

Fig 3 The observed and predicted Pa_{CO_2}–$P\text{E}'_{CO_2}$ differences, plotted against arterial saturation measured by pulse oximetry, for 50 children undergoing cardiac surgery. The solid line represents the regression line for predicted data [regression equation: difference=3.45–0.033(Sa_{O_2}), r=–0.92, P<0.0001] and the broken line represents the regression line for the observed data [difference=4.5–0.038(Sa_{O_2}), r=–0.52, P=0.0001]. The observed values are shown in two groups to indicate which patients had clinical evidence of pulmonary congestion before surgery.

D. Calculate arterial–end-capillary carbon dioxide difference

Multiply C (iii) above by R (assume standard value 0.8 for respiratory quotient).

E. Calculate pulmonary end-capillary bicarbonate carriage

End-capillary bicarbonate=total arterial carbon dioxide content [A (iii)] – carbon dioxide difference (D) – end-capillary carbamino content (B) (ml litre^{-1}).

F. Determine end-capillary $P\text{CO}_2$

Using the derived bicarbonate value from E above, determine the end-capillary $P\text{CO}_2$ from Fig. 1. This approximates to the predicted end-tidal $P\text{CO}_2$ value and can be subtracted from the measured Pa_{CO_2} to determine the predicted Pa_{CO_2}–$P\text{E}'_{CO_2}$.

Methods

After local Ethics Committee approval and written informed consent had been obtained from the parents, 60 children aged between 3 days and 10 yr who were undergoing cardiac surgery were entered into the study. Children with non-cyanotic congenital heart disease and profoundly cyanotic children were included to give a wide range of saturation levels and degrees of shunt. The oxygen saturation in air, measured by pulse oximetry, was recorded for each child before anaesthesia was induced.

Anaesthesia was induced with thiopentone 4 mg kg^{-1} and neuromuscular block obtained with vecuronium 0.1 mg kg^{-1} followed by 0.2 mg kg^{-1} h^{-1}. Anaesthesia was maintained with 0.5–1% isoflurane in oxygen and/or air, supplemented with i.v. alfentanil 10 µg kg^{-1}, followed by an infusion at 2 µg kg^{-1} min^{-1}. All patients were ventilated in a standardized fashion, using a Servo 900C ventilator (Siemens, Bracknell, UK), set to deliver 10 ml kg^{-1} in volume control mode at a rate of 15–25 bpm. The inspiratory time totalled 40% of the respiratory cycle, including a 10% end-inspiratory pause. An end-expiratory pressure of approximately 2 cm H_2O was applied routinely. Intrinsic positive end-expiratory pressure was not measured. During chest opening by thoracotomy or sternotomy, we made simultaneous recordings of oesophageal temperature, haemoglobin concentration and oxygen saturation, oxygen and carbon dioxide tensions in arterial blood, and inspired oxygen and expired carbon dioxide concentrations.

Blood gas and co-oximetry analysis was carried out using a Chiron Diagnostics 865 blood gas machine (Bayer, Newbury, UK). The anaesthetic gases were measured with a Capnomac Ultima gas monitor (Datex Engstrom, Sidcup, UK), which was calibrated against the blood gas machine each morning using a standard gas calibration mixture. The procedure involved initial analysis of the calibration gas by the blood gas machine, and noting the $P\text{CO}_2$ measured by the machine. The capnograph was then calibrated using the calibration gas in the usual way, but entering the $P\text{CO}_2$ concentration as measured by the blood gas machine rather than that printed on the gas canister.

For endotracheal tube sizes 3.0–4.5 mm, gas was sampled for inspired oxygen concentration and end-tidal carbon dioxide concentration using a special connector that allowed gas collection from the proximal endotracheal tube. This allowed greater accuracy of measurement in small subjects.[2] In older children with larger endotracheal tube sizes, normal sidestream gas sampling was used. All blood gas samples were temperature-corrected at analysis.

The data collected were then used to calculate predicted values for Pa_{CO_2}–$P\text{E}'_{CO_2}$ as described previously. Carbon dioxide dissociation curves (Figs 1 and 2) were reproduced from *Nunn's Applied Respiratory Physiology*[5 6] and were enlarged and annotated with grid-lines to aid accuracy. The observed values recorded for arterial and end-tidal carbon dioxide tensions were compared with the predicted values by the use of paired t-tests and regression analysis.

Results

Complete data were obtained from 60 children with ages ranging from 3 days to 10 yr (median 10 months) and saturations in air ranging from 65 to 97% (median 85%). Diagnoses included transposition of the great arteries (nine patients), tetralogy of Fallot (22 patients), hypoplastic left heart syndrome (11 patients), tricuspid atresia (one patient), pulmonary atresia (nine patients), atrioventricular canal defects (two patients), ventricular septal defects (four patients), interrupted aortic arch (one patient) and anomalous pulmonary venous drainage (one patient).

The predicted Pa_{CO_2}–$P\text{E}'_{CO_2}$ value was calculated for each patient as described above. It was found that five

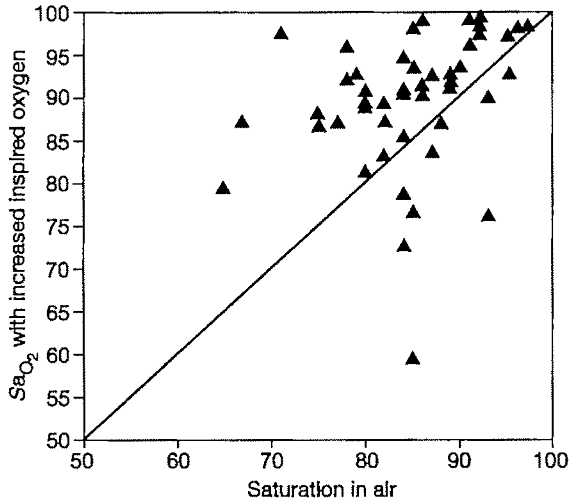

Fig 4 Oxygen saturation when spontaneously breathing air plotted against arterial saturation with increased $F\text{I}_{O_2}$ and controlled ventilation under general anaesthesia, for 50 children with congenital heart disease.

patients within the first 10 had physiologically inconsistent data. One had a very negative Pa_{CO_2}–PE'_{CO_2} and four had a normal Pa_{CO_2}–PE'_{CO_2} with oxygen saturation less than 85%, a situation incompatible with the shunt equation. It was decided to remove these patients from the study, but, in order to reduce bias, data obtained from all of the first 10 patients were eliminated from further analysis.

The observed and predicted values for Pa_{CO_2}–PE'_{CO_2} for the remaining 50 patients were plotted against arterial saturation (measured by the co-oximeter), as shown in Fig. 3. The mean observed Pa_{CO_2}–PE'_{CO_2} difference was 1.07 (SD 0.58) kPa and the mean predicted value was 0.42 (0.29) kPa ($P<0.0001$). The figure shows that many of the observed values for Pa_{CO_2}–PE'_{CO_2} were considerably greater than predicted. Furthermore, the observed Pa_{CO_2}–PE'_{CO_2} exceeded zero in many of the well-oxygenated patients. In fact, the regression line indicated a difference of 0.7 kPa at 100% saturation. The expected negative correlation between Pa_{CO_2}–PE'_{CO_2} and oxygen saturation was apparent for the predicted data; the correlation was less strong for the observed data.

Discussion

The results of this study suggest that the Pa_{CO_2}–PE'_{CO_2} differences in these 50 children with congenital heart disease were frequently greater than that caused solely by right-to-left shunting. The values of Pa_{CO_2}–PE'_{CO_2} predicted from the primary shunt effect show the expected increase in Pa_{CO_2}–PE'_{CO_2} of 0.3–0.4 kPa for every 10% fall in saturation.[3] Clearly, there are other factors contributing to the derangement in gas exchange. In patients with pure right-to-left shunts, these might include the secondary effect of pulmonary hypoperfusion. However, the results are further complicated by the fact that even the well-oxygenated children in our study did not appear to have normal carbon dioxide elimination, in contrast to the results of Fletcher *et al.*[7] In that study, children with normal oxygen saturation were found to have a zero or negligible Pa_{CO_2}–PE'_{CO_2} difference, implying normal lung function. These patients, who had been included in the study in order to establish the Pa_{CO_2}–PE'_{CO_2} in the absence of congenital heart disease, had diagnoses of aortic stenosis, pulmonary stenosis, patent ductus arteriosus and coarctation of the aorta, which were not expected to affect gas exchange. There were no patients in our study group with similarly uncomplicated lesions.

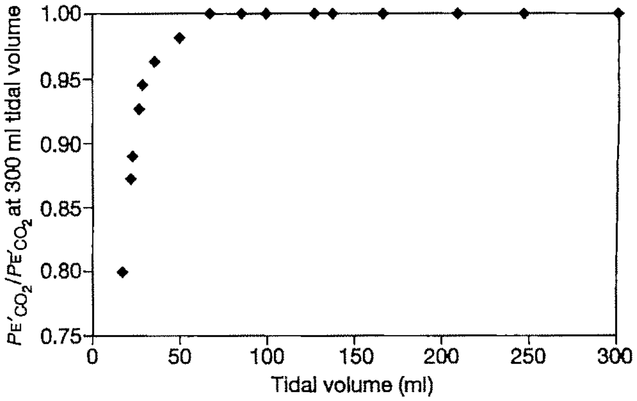

Fig 5 The error in measured end-tidal $P\text{CO}_2$ associated with small tidal volumes, using a carbon dioxide-producing lung model and a calibration test gas. The *y* axis represents the actual value recorded divided by the $P\text{CO}_2$ measured at a control tidal volume of 300 ml.

To find a further explanation for the much increased alveolar deadspace in some apparently well-oxygenated children with congenital heart disease, oxygen saturation while breathing spontaneously in air was plotted against oxygen saturation obtained during controlled ventilation with an increased inspired oxygen concentration (Fig. 4). Most of the children showed an improvement in saturation, implying a degree of ventilation–perfusion mismatch, other than a pure right-to-left shunt effect. In the well-oxygenated patients with significant left-to-right shunting, e.g. those with large ventricular septal defects, pulmonary congestion may have been responsible for the increased alveolar deadspace. Patients whose clinical history was suggestive of moderate to severe pulmonary congestion, typically those with a significant left-to-right shunt, are plotted separately in Fig. 3 to show their influence on the results of the group. Increased pulmonary blood flow causes loss of homeostasis at the alveolar/capillary level and a ventilation/perfusion mismatch.[7] Increased slopes of phase III of the Single Breath Test for carbon dioxide, a sign of increased spread of ventilation/perfusion ratios, can be seen even in children with such relatively mild lesions as atrial septal defect.[7] Very steep phase III slopes have been observed in children with congestive failure.[7]

In addition to these factors, we also explored the possibility that our carbon dioxide analyser had underestimated expired carbon dioxide concentration, in spite of our attempts to sample within the proximal endotracheal tube in small subjects. To investigate this hypothesis, we ventilated a carbon dioxide-producing lung model at different tidal volumes using the ventilator used in the study. This model showed a small carbon dioxide analyser error at tidal volumes below 50 ml, as shown in Fig. 5. This error was not sufficient to explain the observed $P\text{a}_{\text{CO}_2}$–$P\text{E}'_{\text{CO}_2}$ in our patients with normal saturations.

In conclusion, the theoretical model for prediction of $P\text{a}_{\text{CO}_2}$–$P\text{E}'_{\text{CO}_2}$ due to right-to-left shunting in congenital heart disease underestimated the true extent of the derangement of gas exchange in many patients. In addition to the primary, obligatory effect of the shunt, carbon dioxide elimination may be affected by pulmonary hypoperfusion in right-to-left shunts, or by congested pulmonary vasculature in mixed and left-to-right shunts. Hence, it appears that $P\text{a}_{\text{CO}_2}$–$P\text{E}'_{\text{CO}_2}$ in children with congenital heart disease is difficult to predict, especially in the presence of congestive cardiac failure.

In the light of our findings, we suggest that the relationship between pulmonary congestion and $P\text{a}_{\text{CO}_2}$–$P\text{E}'_{\text{CO}_2}$ could be further investigated by performing a similar study on acyanotic children with congenital heart disease, who have been prospectively classified into normal and plethoric groups, by blinded reporting of chest radiographs, elements of the clinical history and the saturation response to increased $F\text{I}_{\text{O}_2}$.

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Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane

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The time course of four EEG effect variables, amplitude in the 2–5 Hz and in the 11–15 Hz band, spectral edge frequency 95% (SEF95), and bispectral index (BIS), in response to increasing concentrations of thiopental, propofol, etomidate, midazolam, or sevoflurane during a 10 min induction of anaesthesia was studied in 25 patients to determine the existence of a biphasic effect and to study the relationship of the EEG effect to the moment of loss of consciousness. A biphasic effect, that is, an initial increase of the effect variable followed by a decrease at higher concentrations, during the transition from consciousness to unconsciousness was found in EEG amplitude (both frequency bands) and in SEF95 for all anaesthetics except midazolam. There was a concentration-related decrease in BIS for all anaesthetics. There was no consistent relationship between the time of occurrence of the peak EEG effect, or the value of the EEG variable and the moment of loss of consciousness. With rapidly changing drug concentrations during the induction of anaesthesia, none of these EEG effect variables could be correlated to the moment of loss of consciousness.

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Processed EEG variables recorded during anaesthesia usually decrease with increasing drug concentrations. However, during the transition from consciousness to unconsciousness, using induction agents, many derived EEG variables show biphasic effects, that is an initial increase of the effect variable followed by a decrease at higher concentrations. This has been observed with thiopental,[1] propofol,[2 3] and sevoflurane.[4] For etomidate, a biphasic effect was described in animals.[5] Midazolam does not appear to induce biphasic EEG changes.[6] The moment of loss of consciousness seems to be related to the occurrence of a maximum effect of the EEG variable, at least when propofol, thiopental, or sevoflurane are used to induce anaesthesia. For the other drugs such a relationship has not been demonstrated. If a biphasic relationship exists for all hypnotic agents, then the reappearance of a maximum EEG height might be used as an indicator of imminent awareness.

We therefore studied the behaviour of four different EEG effect variables during slow induction of anaesthesia with thiopental, propofol, etomidate, midazolam, or sevoflurane with the aims of determining whether a biphasic EEG response was present, and to assess the time to the maximum EEG effect, the times of loss of consciousness, and the relationship between these variables for each study drug. The following variables were analysed: EEG amplitude in two frequency bands, spectral edge frequency 95%, and the bispectral index (BIS), a proprietary composite EEG effect variable designed to have no biphasic response pattern.

Patients and methods

After institutional board approval and obtaining written informed consent, 25 patients, ASA grade I and II undergoing elective vertebral disk surgery entered the study.

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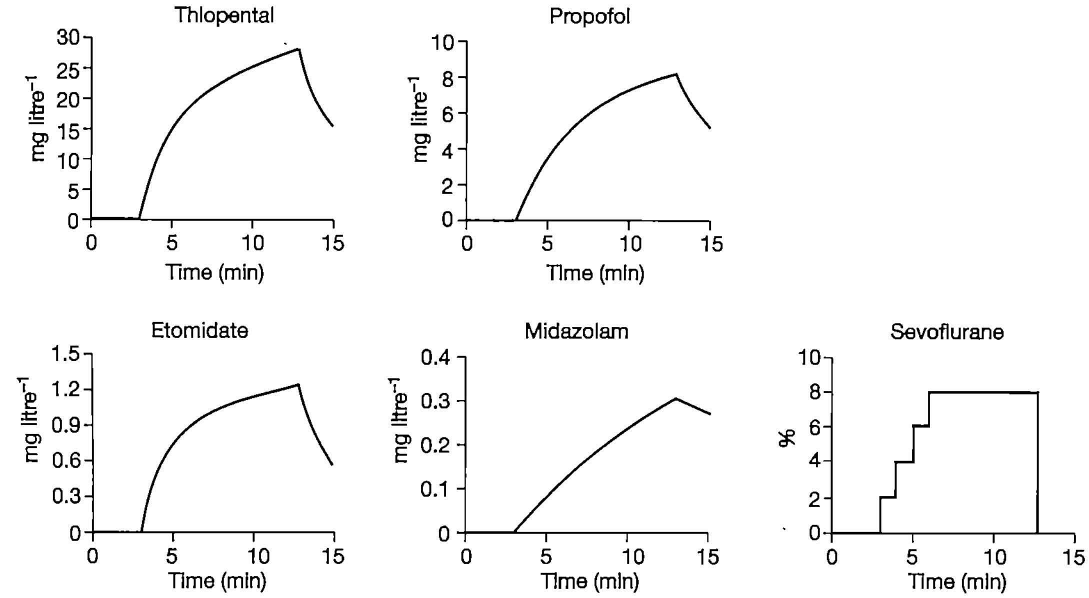

Fig 1 Time course of expected plasma concentrations of thiopentone, propofol, etomidate, and midazolam based on population kinetics (Stanpump) and of sevoflurane concentrations in the fresh gas flow.

Patients with a history of recent intake of drugs that might affect the EEG, an alcohol intake in excess of 30 g day^{-1}, neurological disorders, extreme nervousness, or a contra-indication for one of the study drugs were excluded. No oral intake was allowed after midnight preceding the day of surgery. No pre-medication was administered.

After arrival in the anaesthetic room, an i.v. cannula was inserted and 0.9% saline 500 ml was infused rapidly for fluid loading. Patients were monitored with a three-lead ECG, Sp_{O_2}, and non-invasive arterial pressure measurements performed at 1-min intervals.

Each experiment took place before the start of surgery and lasted 15 min. The study period was divided into a 3 min baseline EEG recording, a 10 min duration EEG recording during study drug administration, and was followed by a 2 min EEG recording without drug administration. The calculation of the dose body weight, corrected for height, was: height (cm)–100=kg body weight. The patients were randomly assigned to one of five groups to receive a 10 min constant rate infusion of thiopental 1 mg kg^{-1} min^{-1}, propofol 0.5 mg kg^{-1} min^{-1}, etomidate 0.06 mg kg^{-1} min^{-1}, midazolam 0.03 mg kg^{-1} min^{-1}, or sevoflurane in oxygen enriched air administered by a circle system with a fresh gas flow of 9 litre min^{-1} and facemask. The sevoflurane concentration of the fresh gas was initially set at 2% and increased every minute by an additional 2% to a maximum of 8%. The last concentration was maintained for a further 7 min. With this dosing regimen we aimed to induce a steadily increasing blood and CNS concentration (Fig. 1).

If spontaneous ventilation became insufficient as indicated by Sp_{O_2} below 92% or signs of upper airway obstruction, a free airway was re-instituted by chin lift and if necessary ventilation was assisted by facemask and oxygen enriched air (40%) to maintain E'_{CO_2} between 4.5 and 6.0 kPa.

EEG was recorded from Cz-Fpz and the M2 (right mastoid)-Fpz2 with an electrode placed between Fpz and Fpz2 as reference. All signals were recorded with the patients in the supine position and eyes closed. The analogue EEG was recorded using the pre-amplifiers of the Lifescan EEG monitor and stored on tape for off-line analysis. For calculation of EEG amplitude in the 0–5 and 11–20 Hz band we used aperiodic analysis[7] (Lifescan, software version 4.3, Diatek, San Diego, CA, USA). For calculation of BIS[8] and spectral edge frequency 95% (SEF95) values we used the Aspect A-1000 EEG monitor (BIS version 3.12: Aspect Medical Systems Inc., Natick, MA, USA). EEG amplitudes in the two frequency bands were calculated from 10-s epochs. Epochs containing an EEG amplitude greater than 30 µV in the 25–30 Hz band were considered to contain too many artefacts and were rejected. The Aspect A1000 low pass filter was set at 30 Hz, the high pass filter was set to 2 Hz. Periods containing artefacts, as indicated by the Aspect A1000 were rejected. Spectral edge smoothing was set at 10 s and BIS smoothing at 15 s. No correction was made for the internal 60 s smoothing of the BIS 3.12. Thus, amplitude and SEF95 data represent EEG data of the preceding 10 s. BIS data represent data from the preceding 75 s.

Responsiveness was determined by testing the response of the patient to simple commands from a pre-recorded tape ('raise your thumb', 'spread your fingers', and 'clench your fist'), given by headphones every 30 s. The first time that the patient did not respond to a verbal command was registered

Table 1 Physical characteristics of the patients and the moment of loss of consciousness after the start of the study. Data are expressed as median (range)

Drug	Male/Female	Age (yr)	Weight (kg)	Height (cm)	Loss of consciousness (min)
Thiopental	2/3	47 (41–50)	75 (62–82)	178 (168–187)	6.6 (5.9–8.6)
Propofol	5/0	32 (18–56)	90 (76–93)	190 (173–192)	6.1 (5.0–6.5)
Etomidate	3/2	43 (39–51)	85 (60–99)	180 (161–187)	5.7 (5.2–6.3)
Midazolam	2/3	36 (21–47)	75 (62–94)	176 (175–188)	7.4 (5.3–10.8)
Sevoflurane	4/1	39 (33–50)	92 (75–105)	186 (178–189)	5.6 (4.8–6.5)

Table 2 Occurrence of biphasic response (*n*); the number of patients losing consciousness (*n*) before and after the peak EEG effect (when present); the median time (min) between peak EEG effect and loss of consciousness; and the median EEG value (range) at the moment of loss of consciousness of the EEG amplitude (µV) in the 2–5 Hz band, the EEG amplitude (µV) in the 11–20 Hz band. Spectral edge frequency 95% (Hz) and BIS. *Different from other drugs ($P<0.05$)

EEG variable	Drug	Biphasic effect (*n*)	Relationship of loss of consciousness to peak EEG effect			EEG value at loss of consciousness	
			Before (*n*)	After (*n*)	Median (min)	Median	Range
Amplitude 2–5 Hz	Thiopental	4	2	1	−1.7	47	34–56
	Propofol	5	3	1	−1.0	40	13–92
	Etomidate	5	4	0	−1.5	173	132–200
	Midazolam	3	1	2	1.3	33	19–39
	Sevoflurane	4	2	0	−0.6	73	29–220
Amplitude 11–20 Hz	Thiopental	5	3	1	−0.7	174	156–315
	Propofol	5	2	0	−0.4	117	66–124
	Etomidate	5	1	2	0.2	153	113–291
	Midazolam	2	2	0	−5.8	205	123–261
	Sevoflurane	5	2	2	0.3	48	28–133
Spectral Edge frequency 95%	Thiopental	5	0	4	2.1	25	20–25
	Propofol	4	0	4	1.4	22	12–25
	Etomidate	5	0	4	1.4	16	13–22
	Midazolam	2	0	2	2.6	24	20–25
	Sevoflurane	5	1	1	0.2	24	13–27
BIS	Thiopental	0				77	63–82
	Propofol	0				77	45–87
	Etomidate	0				66	45–79
	Midazolam	0				77	70–84
	Sevoflurane	0				87*	82–95

as the time of loss of responsiveness (LR). The times of LR were related to the values of the EEG derived variables recorded at that moment.

Definitions and statistical analysis

The EEG response to increasing blood concentrations was considered biphasic if after the start of the drug administration the EEG effect variable increased at least 2 SD above baseline value and, thereafter, decreased 20% below that maximum value.

The patient was supposed to have lost consciousness at the moment of the maximum change of the EEG variable if the moment of LR was less than 30 s different from it.

Data are presented as median and range. EEG data were compared using the Kruskal-Wallis test. $P<0.05$ was considered significant.

Results

Physical characteristics of the patients and the moments of LR are presented in Table 1. EEG data from the Fpz-Cz leads during the infusion showed a similar time course compared with the EEG data from the Fpz2-M2 leads. But EEG data derived from the Fpz2-M2 leads showed more variability than EEG data derived from the FPz-Cz leads during the baseline recording before drug administration. We therefore decided to present only data from the Fpz-Cz leads.

During the administration of thiopental, propofol, etomidate, and sevoflurane the EEG of the patients showed an increase of alpha and beta activity followed by an increase of delta activity and a decrease of beta and alpha activity. All patients in the propofol and etomidate groups and most of the patients in the thiopental group showed a decrease in delta activity by end of the infusion. In the sevoflurane patients, delta activity initially decreased after the maximal effect but did not decrease further despite continued administration. Increasing midazolam doses resulted in increased beta activity.

The EEG amplitude in both frequency bands and SEF95 showed biphasic effects for all drugs except midazolam. The BIS value decreased for all drugs (Table 2, Figs 2 and 3).

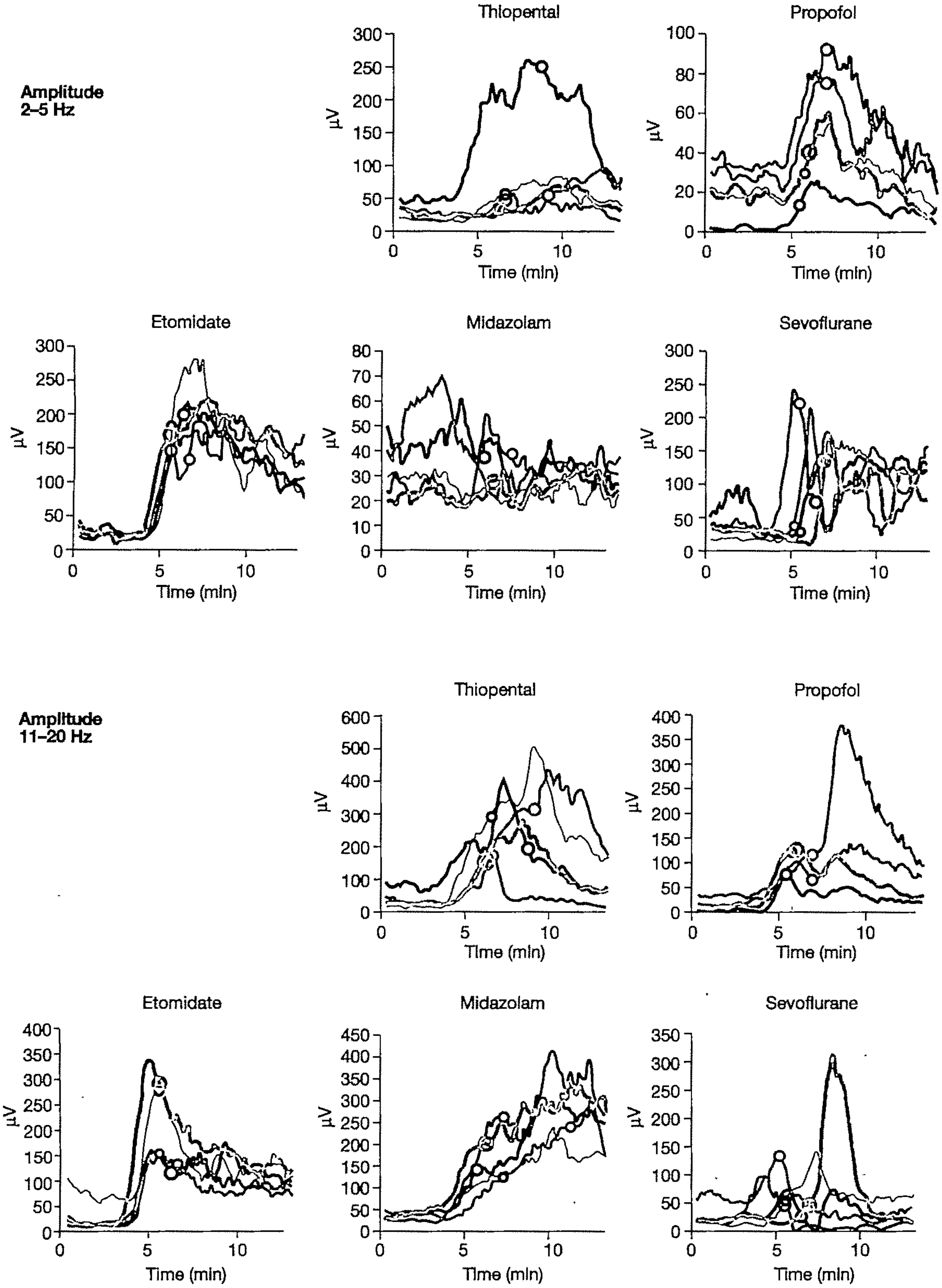

Fig 2 EEG amplitude *versus* time in the 2–5 and 11–20 Hz bands for individual patients. (Open circles indicate the moment of loss of consciousness.)

We did not observe a consistent relationship between the moment of LR and the moment of occurrence of a peak EEG effect. The value of the EEG effect at the moment of LR showed a large variability between patients. BIS values at the moment of LR were significantly higher in the sevoflurane group than in all other groups (Table 2).

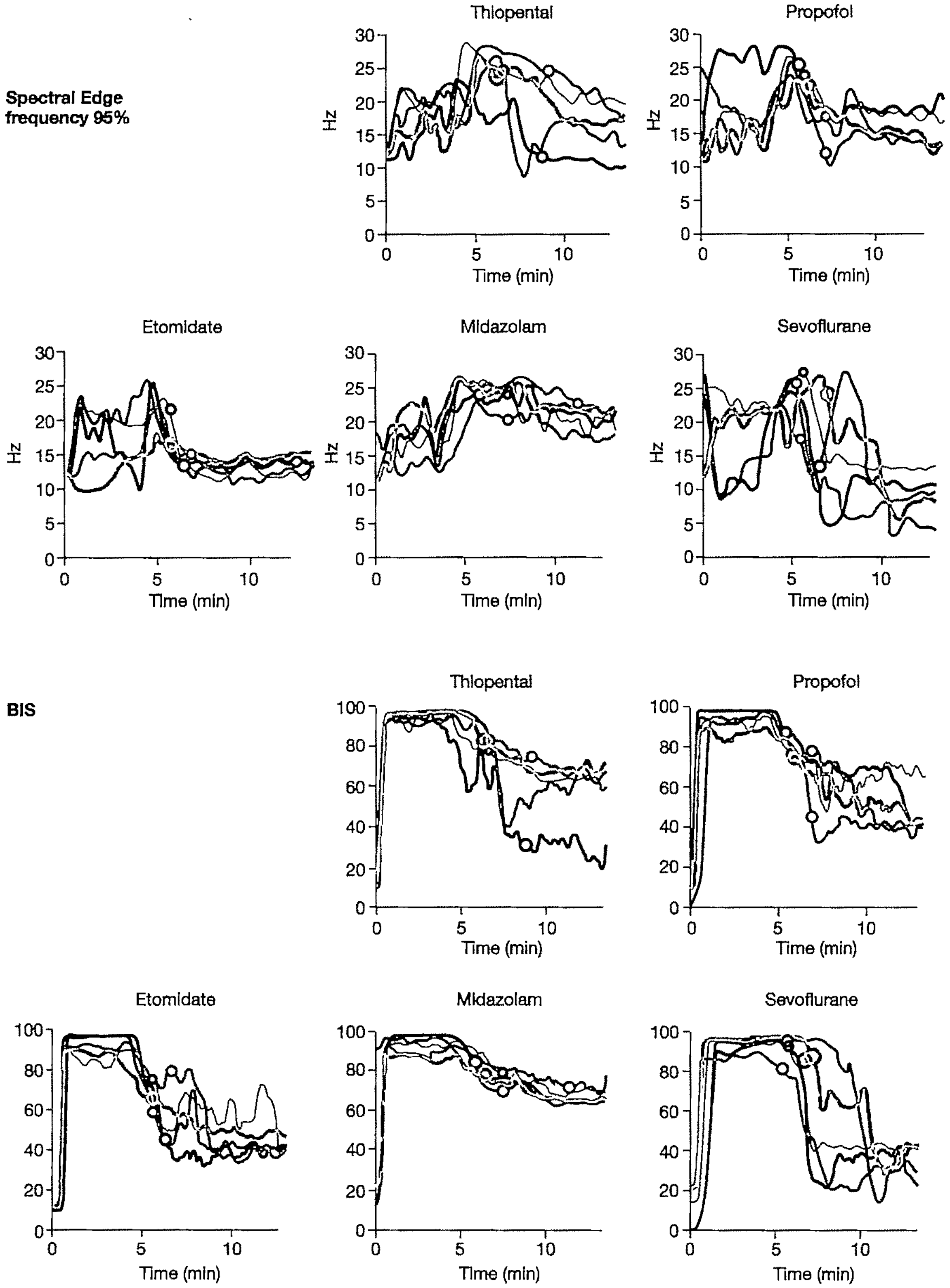

Fig 3 Spectral edge frequency 95% and BIS *versus* time for individual patients. (Open circles indicate the moment of loss of consciousness.)

Discussion

In this study we demonstrated biphasic EEG effects for all the induction agents except for midazolam. Biphasic effects, that is an increase in alpha and beta activity followed by a decrease in alpha and beta activity and a simultaneous increase in delta activity have been observed in the analogue EEG.[9 10] Veselis and co-workers have shown that EEG power in the beta band increases with increasing blood concentrations of thiopental, propofol, and midazolam.[11] They did not observe a decrease of EEG power, but as the drugs were administered in sedative doses only, their patients did not lose consciousness. Other investigators have shown that SEF95 and median frequency decrease when depth of anaesthesia increases.[12–14] Therefore, a peak change in EEG amplitude in the higher frequency bands during the transition from sedation to unconsciousness is very likely. Such biphasic effects have been described for thiopental,[15] propofol,[16] and more recently for sevoflurane.[4] The occurrence of a short-lived peak effect on the EEG might be a marker for the transitional state between consciousness and unconsciousness. If consciousness is lost before the peak change in EEG occurs, that is at a lower blood concentration, during decreasing concentrations a peak EEG effect is coupled with a risk of imminent awareness. Although we observed biphasic effects for all drugs except midazolam during increasing drug concentrations, loss of consciousness did not occur consistently before the maximum change in these EEG variables. This finding limits the potential application of the occurrence of a peak EEG effect to predict imminent awareness. The actual EEG amplitudes and SEF95 values at which consciousness was lost showed a large inter-individual variability. Therefore, absolute values of EEG derived variables are not reliable indicators of loss of consciousness either.

One explanation for the absence of a consistent correlation between the time to loss of consciousness and the value of the EEG effect variable or the time to peak EEG effect for the five drugs might be the biphasic response of the EEG variables to increasing blood concentrations. Such a biphasic response may be the result of simultaneous drug effects both on systems that cause EEG activation and on systems that cause EEG suppression. At lower concentrations, activation is more pronounced than suppression, which results in an increase of amplitude at higher frequencies. At higher concentrations the suppression becomes more evident which results in a decrease of amplitude at higher frequencies and eventually in a decrease of EEG amplitude at lower frequencies. All five drugs suppress consciousness in a dose dependent way. Midazolam does not induce a biphasic EEG response and consciousness was lost before maximal beta activity was reached. With the other drugs one might expect that consciousness would be lost when EEG activity was still increasing in a similar way to midazolam. However, EEG suppression at low concentrations might have counteracted the activation to such an extent that EEG activity had already started to decrease before consciousness was lost. As all drugs have different chemical structures it is likely that there will be differences in the balance of effects on activation and suppression. Therefore, such differences will result in differences in EEG effects at the moment of loss of consciousness.

BIS has been used successfully as an indicator of the level of sedation and hypnosis.[17 18] In the present study we observed that consciousness in the sevoflurane group was lost at higher BIS values than in the other groups (Table 2). This might be caused by the steep decrease in BIS during induction. As a result of the long period over which BIS 3.12 calculates its value, for example, 60+15 s smoothing, the actual BIS value will be overestimated if BIS decreases rapidly. More recent software versions with a shorter calculation epoch may overcome this problem. Another explanation for the higher BIS values observed at the time of LR might be because of the non-specific mechanism of action of sevoflurane inducing loss of consciousness at lower levels of cortical suppression. In a study in which semi-steady state concentrations of sevoflurane were applied,[4] a method that will effectively eliminate averaging effects, the average BIS for preventing response to verbal command was 73. This value is similar to the values found for midazolam, thiopental, propofol, and etomidate in our study. This finding makes the first explanation for the higher BIS values at loss of responsiveness for sevoflurane more likely.

A drawback of the present study is the lack of EEG data during return of consciousness. EEG values at return of consciousness might be different from the EEG values at loss of consciousness and variability might be less. More gradual concentration changes during emergence from anaesthesia will decrease inaccuracy in determination of EEG effect and the determination of the moment of return of consciousness will be less critical. However, other investigators[19] have already indicated that during repeated transitions from unconsciousness to consciousness as the result of repeated interruptions of propofol administration to patients under spinal analgesia, neither SEF95 nor BIS are accurate indicators of imminent awareness.

We conclude that thiopental, propofol, etomidate, and sevoflurane, but not midazolam induce biphasic EEG effects during the transition from consciousness to unconsciousness. There is no consistent time relationship between the peak EEG effect and the moment of LR. In the BIS algorithm, the biphasic response has been linearized effectively, resulting in a progressive decrease of BIS during progressively increasing hypnotic drug concentrations. Both the large inter-subject variability in the values of EEG amplitude and spectral edge, and the relatively long averaging period of BIS, limit the applicability of these variables as markers for imminent consciousness.

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Recovery from propofol anaesthesia supplemented with remifentanil

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We have examined the effects on recovery end-points of supplementation of a propofol-based anaesthetic with remifentanil. After induction of anaesthesia with propofol and remifentanil 1.0 μg kg^{-1}, 15 patients each were randomly allocated to target plasma propofol concentrations of 2, 3, 4 or 5 μg ml^{-1} for maintenance of anaesthesia. Remifentanil was administered by infusion for supplementation in doses required for maintenance of adequate anaesthesia. All patients received 50% nitrous oxide in oxygen and ventilation was controlled. The total amount of drugs used and times to different recovery end-points were recorded. Cognitive function was also assessed using a Mini-Mental State questionnaire. The median dose of remifentanil for maintenance of adequate anaesthesia (excluding the initial bolus dose) in the four groups was 0.21, 0.15, 0.11 and 0.13 μg kg^{-1} min^{-1} respectively (P=0.0026). The median times to eye opening and orientation were shortest in the 2 μg ml^{-1} group [6.0 and 6.5 min, 8.5 and 10.8 min, 13.4 and 15.8 min, and 14.2 and 19.5 min respectively in the propofol 2, 3, 4, and 5 μg ml^{-1} groups respectively (P<0.001)]. The times to discharge from the recovery ward and the Mini-Mental State scores were not significantly different.

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The use of opioids to supplement anaesthesia is a common practice. Remifentanil is a recently introduced opioid analgesic with characteristics of rapid onset and rapid recovery even after prolonged use. The rapid onset results mainly from the short equilibration time between the blood and effect compartments, and the rapid recovery results from the specific kinetic characteristics of this opioid.[1 2] It is metabolized by non-specific esterases and has a high rate of clearance.[3 4] Its other unique feature is a short, unchanging context-sensitive half-time even after prolonged infusion.[2]

It has been shown that the use of higher doses of remifentanil can result in the use of lower doses of propofol to prevent responses to tracheal intubation and surgery.[5] However, it is not known if this has any influence on recovery. The aim of this study was to examine recovery with the use of remifentanil to supplement anaesthesia maintained with different preselected target plasma concentrations of propofol.

Subjects and methods

Sixty adult patients aged 18–65 years and conforming to ASA grades I or II were recruited into the study with their written informed consent and approval from the Research Ethics Committee. They were to undergo elective surgery of at least 30 min duration. Patients on regular sedative or opioid medication were excluded. No premedication was administered.

Anaesthesia was induced and maintained with propofol using a target controlled infusion system (Diprifusor, Zeneca Ltd, Macclesfield, UK).[6 7] The target plasma concentration for induction was set at 4–6 μg ml^{-1}. After loss of the eyelash reflex and verbal response, a bolus dose of remifentanil 1 μg kg^{-1} was administered over 30–60 s and infusion was started at an initial rate of 0.5 μg kg^{-1} min^{-1}. Muscle relaxation, if required, was provided with rocuronium 0.5 mg kg^{-1}. The airway was maintained using a laryngeal mask airway (LMA[†]) or a tracheal tube.

Patients were allocated randomly, using a computer-generated randomization scheme, to target plasma concentrations of propofol (C_T) of 2, 3, 4 or 5 μg ml^{-1} for maintenance of anaesthesia. The infusion rate of remifentanil was adjusted to provide adequate anaesthesia while maintaining the preselected C_T constant. The patients' lungs were ventilated with a mixture of 50% nitrous oxide in

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[†] LMA® is the property of Intavent Limited.

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Table 1 Patient characteristics and duration of anaesthesia. Mean (SD)

	Target plasma concentration of propofol (μg ml^{-1})			
	2	3	4	5
Age (yr)	32 (12)	32 (9)	29 (13)	34 (10)
(range)	(18–57)	(19–51)	(18–64)	(19–50)
Weight (kg)	67 (8)	75 (14)	72 (17)	79 (17)
Height (cm)	172 (8)	171 (11)	174 (11)	172 (11)
M:F	11:4	7:8	10:5	10:5
Duration of anaesthesia (min)	87 (41.1)	79 (38.6)	73 (29.1)	82 (45.1)

Table 2 Doses of remifentanil and propofol (μg kg^{-1} min^{-1}; median and range) administered during the maintenance phase (excluding the induction doses of propofol and remifentanil). $^a P<0.05$ compared with 4 and 5 μg ml^{-1} C_T groups; $^b P<0.001$ compared with 4 and 5 μg ml^{-1} C_T groups; $^c P<0.001$ compared with 5 μg ml^{-1} C_T group. n=15 except where indicated

	Target plasma concentration of propofol (μg ml^{-1})			
	2	3	4	5
Remifentanil	0.2^a (0.08–0.38)	0.15 (0.08–0.32)	0.11 (0.07–0.21)	0.13 (0.05–0.25)
Propofol	0.08^b (0.07–0.08) (n=13)	0.12^c (0.08–0.15)	0.16 (0.15–0.18) (n=13)	0.20 (0.15–0.28) (n=14)

oxygen to maintain normocapnia. Anaesthesia was deemed to be adequate if heart rate and/or arterial pressure remained within 20% of baseline values and there was no movement, lachrymation or sweating in response to surgery. All patients received tenoxicam 20 mg and morphine 10 mg i.v. 15–20 min before the expected end of surgery. The wound was infiltrated with bupivacaine. Neuromuscular block, when instituted, was monitored using a peripheral nerve stimulator and antagonized with neostigmine 50 μg kg^{-1} in a mixture with glycopyrrolate 10 μg kg^{-1}.

Propofol, nitrous oxide and remifentanil were stopped when the last skin suture was applied and recovery from neuromuscular block had been ascertained.

The times to resumption of spontaneous respiration and extubation and/or LMA removal were recorded, as were times to opening the eyes on command, giving the correct date of birth, and orientation for date and time after cessation of all anaesthesia. The doses of remifentanil and propofol administered during the maintenance were recorded. Pain on arrival in the recovery ward was assessed using a 10 cm visual analogue scale (VAS; 0=no pain, 10=worst pain).

A Mini-Mental State (MMS) assessment questionnaire[8] was administered before anaesthesia and 2 h after operation. An assessment was carried out at 4 h if the score had not returned to baseline at 2 h. The assessments of all recovery end-points and MMS assessments were carried out by an observer who was blinded to the group allocation of the patients.

The time when patients were ready for discharge from the recovery ward was recorded by the nursing staff (based on observation of control of pain, absence of emetic sequelae, and satisfactory cardiovascular and respiratory observations). The nursing staff were also unaware of the identity of the groups. The incidence of nausea or vomiting was recorded over the first 24 h period. The patients' sense of well-being was scored the next day during the post-operative visit or by a telephone call (if already discharged) using a 10 cm VAS (0='feels lousy', 10='feels great'). On the next day, patients were also asked three non-leading questions to look for evidence of recall. These were: 'What was the last thing you remember before going to sleep?'; 'Did you have any dreams whilst you were under the anaesthetic?'; and 'What was the first thing you remember when you woke up?'

The continuous data were subjected to one-way analysis of variance, or the Kruskal–Wallis tests, depending on the distributions or significant differences in variances, followed by post-tests if indicated [Bonferroni tests for ANOVA (analysis of variance) and Dunn tests for Kruskal–Wallis tests]. The frequency distributions were subjected to χ^2 tests and differences were considered significant if P was <0.05. The statistical analysis was performed on a desktop computer using the Prism version 3.0 statistical software (Graph Pad, San Diego, CA, USA).

Results

The groups did not differ significantly with respect to age, weight, height and duration of anaesthesia (Table 1). A total of 13 patients (five in the 2 μg ml^{-1} group, one in the 3 μg ml^{-1} group, three in the 4 μg ml^{-1} and four in the 5 μg ml^{-1} group) received muscle relaxation to facilitate surgery and were intubated, the airway being maintained in all other patients using an LMA. The patients were undergoing orthopaedic or general surgery, the distribution being similar within the groups.

Table 3 Times to attainment of different recovery endpoints, and Mini-Mental State (MMS) scores. Median (range). $^a P<0.05$ compared with 4 and 5 μg ml^{-1} C_T groups; $^b P<0.001$ compared with 4 and 5 μg ml^{-1} C_T groups; $^c P<0.05$ compared with 4 and 5 μg ml^{-1} C_T groups. n=15 except where indicated

	Target plasma concentration of propofol (μg ml^{-1})			
	2	**3**	**4**	**5**
Spontaneous respiration (min)	5.0 (2.6–9.2)	6.7 (3.0–10.0)	6.8 (1.0–14.8)	7.3 (0.8–15.3)
Removal of LMA/extubation (min)	6.0^a (3.4–9.7)	8.3 (3.0–12.0)	9.7 (5.0–18.0)	11.1 (0.8–18.5)
Eye opening (min)	6.0^b (4.4–10.8)	8.5^c (5.0–13.5)	13.4 (6.0–23.5)	14.2 (2.9–25.8)
Orientation (min)	6.5^b (4.4–13.5)	10.8^c(7.2–25.6)	15.8 (12.5–28.5)	19.5 (8.9–35.6)
MMS				
Pre-operative	29.5 (26–30)	29 (27–30)	29 (26–30)	30 (26–30)
Post-operative	29 (26–30) (n=14)	29 (28–30)	29 (26–30)	30 (21–30)

Table 4 Post-operative visual analogue score (VAS; median and range) for pain, incidence of post-operative nausea or vomiting (PONV), discharge time from the recovery ward (median and range), and patients' sense of well-being on the VAS (median and range). No significant differences

	Target plasma concentration of propofol (μg ml^{-1})			
	2	**3**	**4**	**5**
Pain (VAS score, cm)	3 (1–6)	3 (1–6)	4 (1–7)	3.5 (1–5)
PONV				
Within 4 h (n)	1/15	1/15	0/15	0/15
Within 24 h (n)	5/15	3/15	8/15	3/15
Time to discharge from recovery ward (min)	100 (36–185)	108 (52–186)	95 (70–160)	110 (34–215)
Feeling of well-being (VAS score, cm)	9 (4–10)	8 (5–10)	8 (1–10)	9.5 (6–10)

The median C_T of propofol for induction of anaesthesia was 6 (range 5–6) μg ml^{-1}, with a mean induction dose of 1.9 (SD 0.37) mg kg^{-1}. The mean time to loss of consciousness was 1.7 (0.5) min.

The doses of remifentanil and propofol used during the maintenance period (excluding the bolus doses given at induction) are given in Table 2. There was a significant difference between the groups in the dose of remifentanil administered [median 0.21, 0.15, 0.11 and 0.13 μg kg^{-1} min^{-1} in the 2, 3, 4 and 5 μg ml^{-1} propofol groups respectively ($P<0.01$)]. The dose of propofol administered was also significantly different; as expected, it increased with increasing target concentration of propofol [0.08, 0.12, 0.16 and 0.20 mg kg $^{-1}$ min^{-1} (median values) in the four groups respectively ($P<0.001$)]. The doses of both remifentanil and propofol in the 13 patients receiving muscle relaxants were similar (remifentanil 0.12–0.30 μg kg^{-1} min^{-1} and propofol 0.08–0.09 mg kg^{-1} min^{-1} in the five patients in the 2 μg ml^{-1} group; remifentanil 0.15 μg kg^{-1} min^{-1} and propofol 0.11 mg kg^{-1} min^{-1} in the one patient in the 3 μg ml^{-1} group; remifentanil 0.08–0.16 μg kg^{-1} min^{-1} and propofol 0.15 mg kg^{-1} min^{-1} in the three patients in the 4 μg ml^{-1} group; and remifentanil 0.05–0.25 μg kg^{-1} min^{-1} and propofol 0.19–0.23 mg kg^{-1} min^{-1} in the four patients in the 5 μg ml^{-1} group).

The times to various recovery end-points are given in Table 3. In the propofol 2 μg ml^{-1} C_T group (who received the highest dose of remifentanil), the LMA was removed or extubation was carried out significantly earlier (median time 6.0, 8.3, 9.7 and 11.1 min respectively in the 2.0, 3.0, 4.0 and 5.0 μg ml^{-1} propofol groups; P=0.01). The corresponding median times to eye opening and orientation were 6.0 and 6.5, 8.5 and 10.8, 13.4 and 15.8, and 14.2 and 19.5 min respectively ($P<0.001$ for both end-points). MMS scores were not significantly different either between the groups or between the pre-operative and post-operative assessments within each group. One patient in the 5 μg ml^{-1} C_T group had an MMS score of 21 at 2 h which returned to the pre-operative baseline value of 26 by 4 h.

There was no significant difference between the groups in the VAS pain scores on arrival in the recovery ward (Table 4). In the first 4 h after anaesthesia, only two of the 60 patients complained of nausea or vomiting, although the number increased to 19 in the first 24 h. There was no significant difference between the groups. There was no significant difference between the groups in the time for readiness to discharge from the recovery ward (median time 100, 108, 95 and 110 min in the 2, 3, 4 and 5 μg ml^{-1} C_T groups respectively). There was also no significant difference between the groups in the patients' sense of well-being on the day after surgery.

Four patients developed heart rates of 40–45 beats min^{-1}, but this was not associated with any changes in arterial pressure and did not require treatment. One patient each in the propofol 2 and 3 μg ml^{-1} C_T groups developed chest wall rigidity requiring administration of succinylcholine and tracheal intubation; anaesthesia and surgery were otherwise uneventful. No patient had recall of any intra-operative events when asked the next day.

Discussion

The results of this study show that adequate anaesthesia can be maintained by using different proportions of the hypnotic and the opioid. It is also evident that the use of a short-acting opioid, such as remifentanil, when given at a higher dose in association with a lower dose of the hypnotic (propofol) results in a more rapid, early recovery.

It has been shown previously that opioids such as fentanyl and alfentanil exert a propofol-sparing effect, reducing its dose for maintenance of anaesthesia.[9 10] We have demonstrated a propofol-sparing effect of remifentanil that allows a lower propofol C_T to be used for maintenance of anaesthesia. However, the propofol-sparing effect of fentanyl was not associated with an improvement in recovery time.[9] While propofol and alfentanil can be administered at different plasma concentrations to give an ideal ratio that could be used to give the most rapid return of consciousness, it requires a complicated step-down regime for both agents.[10] Vuyk *et al.*, using a computer simulation program, have also suggested that the propofol concentrations that allow the most rapid return of consciousness are lower when it is administered with remifentanil than when combined with alfentanil or fentanyl.[11]

Remifentanil is a unique drug, with rapid onset that allows rapid intraoperative titration dependent upon clinical needs, and rapid and predictable offset. It also has a short and constant context-sensitive half-life.[2 12] Regardless of the duration of infusion, the decrease in plasma concentration to 50% has a time of 3.6 min.[12] These characteristics allow uncomplicated changes in infusion rates with rapid effect, making remifentanil an ideal adjunctive agent for i.v. anaesthesia. The present study has clearly shown the influence of its use on early recovery.

As expected, patients in the groups receiving the higher C_Ts of propofol received significantly more propofol and those receiving the lower concentrations received significantly more remifentanil. By changing the balance of the anaesthetic agents and maintaining the same qualitative anaesthetic, patients in the 2 and 3 $\mu g\ ml^{-1}$ C_T groups had more rapid recovery and return of orientation. This was obviously because of the unique characteristics of remifentanil. However, in spite of early post-operative recovery in patients given the higher supplementation doses of remifentanil, there were no significant differences in the times when patients were ready for discharge from the recovery ward (although there was a trend towards a shorter time in the 2 $\mu g\ ml^{-1}$ group) or in the patients' perception of well-being. This has been shown in another study recently, in which the use of remifentanil was associated with faster, early recovery but with no difference in discharge from the recovery ward and patient satisfaction.[13] This indicates a useful effect of remifentanil supplementation only in the early post-operative period. This is perhaps what would be expected from a drug with a short duration of action. The actual discharge from the recovery ward may be influenced by other factors, such as post-operative pain or nausea and vomiting. The nurses' preconception of a minimal period of stay in the recovery ward may also play a role. It is our impression that, despite the availability of more rapidly-acting anaesthetic agents and faster recovery times, the actual time of discharge of patients from the recovery ward may be delayed by paperwork and logistic difficulties such as portering and the availability of surgical ward nursing staff to accept patients, factors over which anaesthetists may have little control. This has also been noted by others[14 15] and needs to be examined if full use is to be made of the advantages of new drugs and techniques. Nevertheless, an advantage in terms of early recovery is also useful, and would result in less need for intensive nursing supervision.

The MMS assessment has been used previously by Chung in assessing the return of higher mental function in the elderly after neuroleptanaesthesia.[8] We, however, found little difference in these scores between the groups pre-operatively, and little difference between pre- and post-operative scores within each group. The MMS score may be an insensitive measure of recovery after administration of short-acting agents, or it may be more useful when applied at an earlier time. No patient had recall of any intra-operative events, although most could recall waking up in the operating theatre after surgery.

A possible disadvantage of the use of remifentanil as the intra-operative opioid is the absence of immediate post-operative analgesia. This was taken into consideration in the present study by administration of morphine and tenoxicam, and infiltration of the wound with bupivacaine before termination of anaesthesia. This resulted in most patients being comfortable in all groups (no significant difference in VAS scores) but did not affect post-anaesthetic recovery, and may be of advantage in moderately painful procedures performed on day-case surgical patients.

In conclusion, the results of our study show shorter recovery times when maintenance of anaesthesia is changed from using a higher dose of propofol with a lower dose of remifentanil to a regime with a lower dose propofol and a higher dose of remifentanil. However, the advantages are limited to early recovery.

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Post-operative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurane and spinal anaesthesia

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We prospectively studied the post-operative recovery profile of 28 ex-premature infants undergoing inguinal herniotomy. All infants had a post-conceptual age of less than 46 weeks at the time of surgery and were randomized to receive either sevoflurane (group 1, 14 patients) or spinal anaesthesia (group 2, 14 patients). All patients received supplemental caudal analgesia before skin incision. Cardiorespiratory function was continuously recorded in all patients before and after surgery. A blinded observer analysed each paired recording for predefined episodes of apnoea, hypoxaemia or bradycardia and the reports were used to compare the two groups. Spinal anaesthesia was attempted unsuccessfully in four patients in group 2. Five patients in group 1 demonstrated an 'excess' number of episodes (median 4, range 3–12) of clinically silent post-operative cardiorespiratory complications. ('Excess' in our study was defined as a 3-fold or greater increase in the number of post-operative episodes of bradycardia or apnoea relative to pre-operative occurrence). Three of these patients had pre-existing abnormal respiratory function and accounted for 80% of the episodes (26/32) of post-operative bradycardia and all five episodes of post-operative apnoea identified. All episodes of bradycardia and apnoea were temporally unrelated. None of the remaining patients in group 2 demonstrated an unacceptable number of post-operative cardiorespiratory complications. Our limited study suggests that general anaesthesia with an inhalational agent such as sevoflurane may induce or unmask abnormalities of cardiopulmonary function in predisposed infants. Spinal anaesthesia may be preferable but it is potentially stressful for the infant and associated with a clinically significant failure rate.

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Inguinal hernias are common in former pre-term infants and require early repair to avoid the risks of incarceration.[1 2] However, the risk of life-threatening apnoea after surgery is significant in this group regardless of the anaesthetic technique used.[2–4] The reported incidence of post-operative respiratory dysfunction ranges from 20 to 50% and reflects the variation in both anaesthetic technique and study design.[2 5–9] Spinal anaesthesia appears to reduce the risk of respiratory dysfunction but does not abolish it.[2 8] Moreover, the technique requires considerable expertise, is contraindicated in some infants, has a reported failure rate of 10–20%, and can be of insufficient duration for surgery. As a result, the technique may need to be abandoned or supplemented with sedatives or anaesthetic agents, negating any potential benefits.[2 7] Therefore, despite the perceived advantages of this approach, awake spinal anaesthesia has not gained universal acceptance amongst paediatric anaesthetists and many institutions have rejected it.[2 3 10]

The introduction into paediatric practice in the UK of sevoflurane and desflurane with their properties of enhanced recovery characteristics may offer a more practical solution. In neonates undergoing pyloromyotomy, it has been observed that recovery after desflurane is twice as fast as isoflurane with less post-operative ventilatory disturbance.[11] Sevoflurane has similar recovery characteristics but unlike desflurane provides excellent conditions for inhalation induction.[12 13]

We therefore designed a prospective, randomized pilot study that would reflect both clinical practice at our institution and explore the hypothesis that the 'recovery

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profile' after sevoflurane anaesthesia is comparable with that after spinal anaesthesia. With neither group experiencing an increase in the number of episodes of apnoea, hypoxaemia or bradycardia relative to pre-operative levels.

Patients and methods

After obtaining Ethical Committee approval and informed parental consent we studied 28 patients undergoing inguinal herniotomy. All infants had been born at less than 36 weeks gestation and had a post-conceptual age (PCA) of less than 46 weeks at the time of surgery. Infants with pre-existing cardiac, neuromuscular or metabolic diseases were excluded from participation in the study. Pre-operative haemoglobin concentration and a history of 'pre-existing abnormal respiratory function', with or without an on-going requirement for supplemental oxygen therapy, were noted (Tables 1 and 2). We defined 'pre-existing abnormal respiratory function' as the persistence of clinical features of respiratory distress in association with an abnormal chest radiograph beyond the first 28 days of life, either occurring alone or in combination with a 'current' history of apnoea (i.e. episodes witnessed within the 2 weeks before surgery).

Patients were allocated randomly, using random number tables, to receive either sevoflurane anaesthesia with caudal analgesia (group 1) or awake spinal anaesthesia with caudal analgesia (group 2). No sedative pre-medication was administered but all patients received paracetamol 15 mg kg^{-1} per rectum 1 h before surgical incision.

In group 1, general anaesthesia was induced with a 2 MAC equivalent value for age of sevoflurane in 100% oxygen (1 MAC=3.2% in neonates).[14,15] Atracurium 0.5 mg kg^{-1} was used to provide muscle relaxation for tracheal intubation and the lungs were ventilated to normocapnia with an end-tidal sevoflurane concentration of 0.5–1.0 MAC in an air–oxygen mixture until completion of skin closure.

In group 2, spinal anaesthesia was established with 0.5% bupivacaine 1 mg kg^{-1}. Patients were placed in the left lateral position and a 25-gauge short bevelled spinal needle inserted in the midline through either the fourth or fifth lumbar interspace until free flowing cerebrospinal fluid was obtained. To ensure that the groups were comparable to one another in terms of the duration and intensity of analgesia provided in the initial post-operative period, both patient groups received before skin incision a single injection of 0.25% bupivacaine 2 mg kg^{-1} through a 22-gauge cannula inserted into the caudal epidural space.[16,17] 'Induction to incision' (group 1, start of gaseous induction to surgical incision; group 2, skin penetration with spinal needle to surgical incision) and 'incision to closure' times were recorded for both patient groups (Table 1).

Upon completion of skin closure, sevoflurane administration in group 1 was discontinued and residual neuromuscular block antagonized with neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1}.

Table 1 Patient characteristics and intra-operative data. A comparison of post-conceptual age (PCA), gestational age (GA), weight (Wt), pre-operative haemoglobin (Hb) and anaesthetic time (induction–skin closure) for the two groups (median [range]). There was no significant difference between the groups with regard to and variable. *n*=number of patients

	Group 1 (*n*=14) sevoflurane	**Group 2 (*n*=10) spinal**
PCA (weeks)	38 [32–46]	40 [36–44]
GA (weeks)	30 [23–35]	8 [26–33]
Wt (kg)	2.6 [1.2–3.5]	2.8 [1.7–3.6]
Hb (g dl^{-1})	10.2 [9.0–13.4]	10.9 [9.6–12.7]
Bilateral repairs (*n*)	7	5
Induction–incision (min)	23 [16–29]	19 [11–28]
Incision–closure (min)	26 [10–45]	28 [12–48]

Table 2 Number of episodes of pre- and post-operative apnoea and bradycardia recorded in each subject. a, apnoea lasting 15 s or longer; b, bradycardia (less than 100 beat min^{-1}) for at least 5 s. Y, yes; N, no. *Subjects identified as exhibiting an 'excess' of post-operative cardiorespiratory complications

Subject no.	**Group**	**Abnormal respiratory function/oxygen therapy**	**Number of episodes**			
			Pre-op 12 h		**Post-op 12 h**	
			a	b	a	b
1*	1	Y/Y	–	–	–	10
2	1	N	–	–	–	–
4	1	N	–	–	–	–
7	1	Y	–	5	–	–
8	1	Y/Y	–	–	–	–
11	1	N	–	1	–	–
14*	1	Y/Y	–	3	4	12
16	1	N	–	–	–	1
17*	1	N	–	1	–	3
18*	1	N	–	1	–	3
22*	1	Y/Y	–	–	1	4
24	1	N	–	–	–	–
26	1	N	–	–	–	–
28	1	N	–	1	–	1
6	2	N	–	–	–	–
10	2	Y/Y	–	1	–	1
12	2	N	1	2	–	1
13	2	Y	–	1	–	1
15	2	N	–	–	–	–
20	2	N	–	1	1	2
21	2	Y/Y	–	2	–	–
23	2	Y/Y	–	1	–	1
25	2	N	–	–	1	2
27	2	N	–	–	–	–

All patients were monitored for a 12 h period pre- and post-operatively using a portable three channel continuous cardiorespiratory monitor (Nellcor Puritan-Bennett EdenTrace II Plus) with internal memory multi-channel recorder interfaced with an EdenTec 3310 Assurance monitor. This integrated monitoring system provided continuous contemporaneous recordings of respiratory effort and pattern (impedance pneumography/airflow thermistor), heart rate (ECG) and haemoglobin oxygen saturation (pulse oximeter) for each patient. In order to allow each patient to

Table 3 Comparison of median [range of medians] pre- and post-operative cardiorespiratory changes within and between the groups. There was no statistically significant difference either within or between the groups (P>0.05). *Patient 22

	Sevoflurane group 1 (n=14)		**Spinal group 2 (n=10)**	
	Pre-op	**Post-op**	**Pre-op**	**Post-op**
Sp_{O_2} (%)	97 [88*–99]	97 [90*–100]	96 [93–99]	96 [92–99]
Heart rate	150 [128–179]	155 [137–176]	142 [134–150]	150 [138–168]
Per cent time Sp_{O_2} <90%	6 [1–63*]	6 [0–48*]	6 [0–17]	5 [2–28]
Number of episodes of Sp_{O_2} <90% h^{-1}	9 [3–20]	10 [4–14]	6 [2–11]	7 [3–16]

act as their own control, those infants presenting for surgery with an on-going oxygen requirement were prescribed a constant flow rate of supplemental nasal oxygen for the duration of the perioperative period of cardiorespiratory monitoring (Table 2).

Using the following analysis criteria, each computer-generated printout was individually analysed for evidence of either movement artefact or electrode dislodgement by an investigator (J.M.W.) blinded to the anaesthetic technique used. An event was defined as being a result of an artefact if one or both of the following occurred: (1) one or more of the above waveforms out of range or unrecognizable and (2) a Sp_{O_2} less than 90% for more than 20 s with no associated bradycardia or apnoea.

Clinical significance was defined as a bradycardia of less than 100 beat min^{-1} for at least 5 s, a haemoglobin oxygen saturation (Sp_{O_2}) of less than 90% for more than 10 s and apnoea as a sustained respiratory pause of 15 s or longer, or less than 15 s if accompanied by an Sp_{O_2} less than 90% or bradycardia. These manually validated reports, in which each subject acted as their own control, were then used to draw comparisons between the two groups in terms of the number of 'excess' post-operative cardiorespiratory complications recorded. 'Excess' in our study was defined as a 3-fold or more increase in the number of post-operative episodes of bradycardia or apnoea relative to pre-operative occurrence.

In accordance with departmental guidelines regarding the routine post-operative observation and care of infants potentially at risk of respiratory dysfunction, real-time apnoea monitoring (Graseby MR10 respiration monitor) in combination with nurse observation was undertaken for all study patients in the post-operative period.

In view of the small sample size, data are reported as median (range). Comparison of cardiorespiratory changes within and between groups (Table 3) was performed using the Mann-Whitney U test. A P<0.05 was considered statistically significant.

Results

Twenty-eight patients were recruited into the study. Both groups were comparable in terms of PCA, gestational age (GA), weight (Wt), pre-operative haemoglobin level (Hb) and anaesthetic time (induction–skin closure) (Table 1).

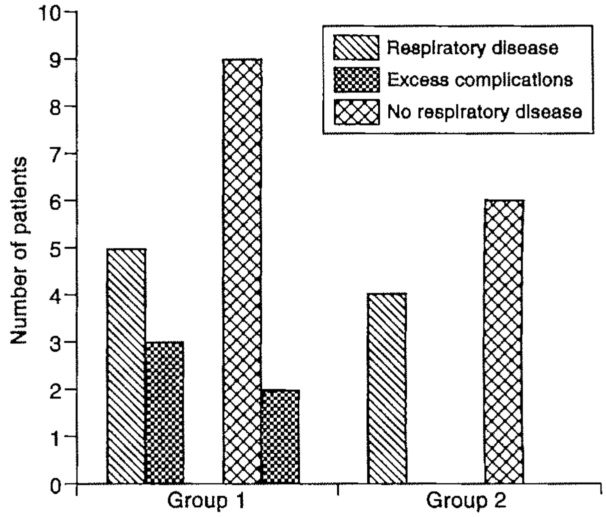

Fig 1 Group distribution of 'excess' post-operative cardiorespiratory complications related to pre-operative respiratory function.

Table 4 Total number of post-operative episodes of apnoea and bradycardia recorded in relation to the pre-operative respiratory function of those patients in group 1, subsequently identified as exhibiting an 'excess' of post-operative cardiorespiratory complications

	Abnormal respiratory function	**Normal respiratory function**
Number of patients	3	2
Episodes of apnoea	5	0
Episodes of bradycardia	26	6

Five patients (four receiving supplemental oxygen) in group 1 and four patients (three receiving supplemental oxygen) in group 2 fulfilled the study definition of 'pre-existing abnormal respiratory function' (Table 2). No patients had a current history of apnoea or were receiving respiratory stimulants in the 2-week period before surgery.

Spinal anaesthesia was attempted unsuccessfully in four patients in group 2 (28% failure rate). All had normal respiratory function and went on to have their surgery successfully completed under general anaesthesia but were excluded from further analysis.

Median pre- and post-operative values for heart rate, Sp_{O_2}, relative duration of a decrease of Sp_{O_2} (per cent time

Sp_{O_2} less than 90%) and number of episodes of desaturation (Sp_{O_2} less than 90% h^{-1}) in group 1 were comparable to values recorded in group 2 (Table 3).

In group 1, three out of the five patients with pre-existing abnormal respiratory function and two out of the nine patients with normal respiratory function experienced an excess of post-operative cardiorespiratory complications (Table 2). In contrast, none of the 10 patients in group 2 exhibited an excess of post-operative complications when compared with their respective pre-operative recordings (Fig. 1).

Table 4 relates the total number of post-operative episodes of apnoea and bradycardia recorded to the pre-operative respiratory function of those patients in group 1 identified as exhibiting an excess of post-operative cardiorespiratory complications (Table 2). The three patients with abnormal respiratory function accounted for 80% of the episodes (26/32) of post-operative bradycardia and all five episodes of post-operative apnoea identified. All recorded episodes of apnoea (five in group 1 and two in group 2) were temporally unrelated to the recorded episodes of bradycardia and haemoglobin oxygen desaturation (Sp_{O_2} less than 90%) (Tables 2 and 3).

One patient in group 1 (patient no. 22), presented for surgery with a median Sp_{O_2} less than 90%. This level of hypoxaemia persisted throughout the post-operative period and accounted for the wide range in the duration of hypoxaemia (median per cent time Sp_{O_2} less than 90%; 63 versus 48%) recorded for each study period (Table 3).

The concurrent use post-operatively, as per hospital policy, of real-time apnoea monitoring in combination with nurse observation failed to detect any of the above recorded episodes of cardiorespiratory disturbance. All resolved spontaneously without intervention.

Discussion

We have endeavoured to design a study that reflects as closely as possible clinical practice at The Royal Hospital for Sick Children in Bristol. After the work conducted at our institution by Peutrell and Hughes, a combined approach of separate spinal and caudal epidural injections has been the preferred method of anaesthesia for those infants presenting for lower abdominal surgery who are thought to be at risk of post-operative cardiorespiratory complications.[17] We have found this approach provides anaesthesia of a sufficient quality and duration to permit the completion of bilateral inguinal herniotomies without the need for additional incremental boluses of local anaesthetic. The dosing regime (bupivacaine 3 mg kg^{-1}) in the awake-spinal–caudal group has been used without untoward sequelae at our institution for at least the last decade. It is less than the 3.8 mg kg^{-1} dose used by Gunter and colleagues[18] to establish single injection caudal epidural anaesthesia and compares favourably with the mean total dose of bupivacaine 2.8 mg kg^{-1} (range 2.5–3.7 mg kg^{-1}) used by Peutrell and Hughes in their study of a combined spinal–epidural technique.[17]

Several studies to date have determined that the incidence of clinically significant post-operative apnoea falls exponentially with time from the completion of surgery.[2 6 19] Proposed aetiological factors for this include the hang-over effect of residual anaesthetic agents combined with an elevated plasma level of circulating endorphins. The contribution of the latter is in turn related to the intensity and duration of the surgical insult.[5 19] By attempting to ensure that both groups were comparable in terms of the duration and intensity of analgesia provided, we hoped to be able to detect in the initial post-operative period any excess cardiorespiratory complications attributable to residual anaesthesia alone.

The results of our pilot study suggest that despite the enhanced recovery characteristics of sevoflurane, the recovery profile in this vulnerable age group may not be comparable to that of 'awake' spinal anaesthesia in all infants. However, balanced against this, was our inability to establish spinal anaesthesia in four subjects (28%), despite the technique being performed by experienced paediatric anaesthetists. This highlights the considerable expertise and practice required and is one of the primary reasons why the seemingly advantageous procedure of spinal anaesthesia has not gained universal acceptance in many paediatric institutions.[3 7] These findings need to be interpreted within the context of the limited size of the study and, therefore, require further comment.

Viewed as a whole, the recovery profile of both groups appeared comparable with neither group experiencing a significant number of episodes of hypoxaemia (Sp_{O_2} less than 90% h^{-1}) relative to pre-operative levels (Table 3). It must, however, be appreciated that these results were based on computer generated recordings and are therefore susceptible to artefact.[20] The addition of real-time video surveillance in a sleep study unit would have helped to limit the impact of the undefined noise-to-signal ratio of the recording system, but because of the unpredictable scheduling of surgery this was not a feasible option. An observer blinded to the anaesthetic technique used, therefore checked the validity of each recording manually.

Five out of the 14 patients (36%) in group 1 compared with none of the 10 patients in group 2 exhibited an excess of post-operative cardiorespiratory complications (Table 2). In patients with pre-existing abnormal respiratory function, three out of five patients in group 1 demonstrated an excess of post-operative cardiorespiratory complications compared with none of four in group 2 (Fig. 1). We propose a number of possible explanations to account for this difference between the groups.

First, with reference to a standard premature infant growth chart, we established that those patients in group 2 with pre-existing abnormal respiratory function were born 'small-for-gestational-age' (less than 10th percentile) as opposed to 'appropriate-for-gestational-age' (10th–90th percentile) when compared with the birth weights of corresponding patients in group 1.[21] Coté and colleagues have determined that when controlled for age, haematocrit (greater than 30%) and institution, small-for-gestational-age infants seem to have a somewhat lower risk of post-operative apnoea.[19]

Second, it is possible that the observed differences between the two subgroups are purely a function of the level of monitoring. In our study, the concurrent use of standard real-time post-operative apnoea monitoring in combination with nurse observation, as per hospital policy, failed to detect any of the subsequently computer identified adverse episodes (Tables 2 and 4). This raises the interesting question whether cardiorespiratory complications only detectable by sophisticated techniques are clinically important; particularly when they appear to resolve spontaneously without intervention.

Third, the study of relatively rare events requires a large patient population that is impossible to acquire at any one institution. Using a statistical approach recommended by Hanley and Lippman-Hand, Coté and colleagues determined that a sample size of at least 300 patients would be necessary to detect a 1% incidence of apnoea with 95% confidence in a particular age group.[19 22] Therefore, considering the limited size of this pilot study, it is possible that we have rejected our hypothesis when it is, in fact, true. In other words, the observed difference between the two groups is not significant and our results are, at best, inconclusive.

Impedance pneumography is the most widely used form of respiratory monitoring but has limitations for detecting obstructive airway problems and a high incidence of false alarms.[20] The importance of upper airway obstruction in the pathophysiology of apnoea and bradycardia is well described in infants with periodic breathing and low PCA.[23 24] It is, therefore, reasonable to conclude that general anaesthesia, which can decrease upper airway muscle tone, may contribute to the development of cardiorespiratory complications in susceptible infants.[9] Given the limitations of impedance pneumography for detecting obstructive airway problems, this may account for why the incidence of apnoea was comparable between the groups and may also, in part, explain the excess of temporally unrelated episodes of bradycardia in group 1 (Tables 2 and 4).

It is clear even from our limited study that post-operative cardiorespiratory complications occur frequently in former pre-term infants after relatively minor surgical procedures. Allowing for the high detection rate with sophisticated computer-assisted continuous recording devices, it is also apparent that general anaesthesia even with modern evanescent agents such as sevoflurane can induce or unmask abnormalities of cardiopulmonary function in predisposed infants. Recent work by O'Brien and colleagues has been more encouraging.[12] They suggest that desflurane, in terms of the quality of recovery that it offers, may be the most appropriate potent inhalational agent with which to maintain general anaesthesia in high risk infants.

In conclusion, spinal anaesthesia may be preferable to general anaesthesia for ex-premature infants undergoing lower abdominal surgery within the first weeks of life. But until this has been demonstrated in large prospective, controlled studies in comparison with modern low solubility potent inhalational agents, we will continue to have reservations about routinely subjecting our patients to an awake technique that is potentially stressful for the infant and associated with a clinically significant failure rate.

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Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during Caesarean section

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Pre-emptive intramuscular (i.m.) vasopressors were evaluated in 108 patients undergoing elective Caesarean section under spinal anaesthesia, assigned to four groups in a randomized, double-blind, placebo-controlled study. Group 1 received pre-emptive phenylephrine 4 mg i.m., group 2 received phenylephrine 2 mg i.m., group 3 received ephedrine 45 mg i.m., while controls received an i.m. injection of saline, all given immediately after induction of spinal anaesthesia. Hypotension was defined as a 25% decrease in mean arterial pressure (MAP). Rescue intravenous (i.v.) boluses of ephedrine were given if the patient was hypotensive or reported nausea, vomiting or dizziness. The incidence of hypotension was 33% in the phenylephrine 4 mg group compared with 70% in the control and phenylephrine 2 mg groups (P=0.03), and 48% in the ephedrine 45 mg group. The phenylephrine 4 mg and ephedrine 45 mg groups had a significantly lower percentage reduction in MAP (–21 (SD 14)% and –22 (14)%) compared with controls (–32 (18)%, P=0.04). They also had a lower total dose of rescue i.v. ephedrine (15.7 (15.7) mg and 15.8 (15.6) mg) compared with controls (28.8 (20.6) mg, P=0.02). We conclude that pre-emptive i.m. phenylephrine 4 mg and ephedrine 45 mg reduce the severity of hypotension and the total dose of rescue i.v. ephedrine during spinal anaesthesia for Caesarean section.

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The incidence of hypotension during spinal anaesthesia for Caesarean section is reported to be as high as 80%, despite fluid preload, lateral uterine displacement and use of vasopressors.[1] Maternal hypotension is associated with the distressing symptoms of dizziness, nausea and vomiting, and may also interfere with the surgical procedure.[2] Lateral uterine displacement using a 15° tilt is essential in parturients to prevent the 'supine hypotensive syndrome' whereby compression of the inferior vena cava by the gravid uterus leads to reduced venous return and subsequent hypotension. Although fluid preloading is still widely used, its place in the management of hypotension induced by spinal anaesthesia has been questioned.[3] The management of choice of this common problem is the use of intravenous (i.v.) vasopressors as required. Ephedrine, an indirectly acting sympathomimetic amine, is probably the vasopressor of choice in obstetric anaesthesia. Although ephedrine has mixed α- and β-adrenoreceptor activity, it maintains arterial pressure mainly by increases in cardiac output (CO) and heart rate as a result of its predominant activity on β_1-adrenoreceptors.[4] Phenylephrine, an α_1-adrenergic agonist whose action would be expected to counteract the decrease in systemic vascular resistance induced by spinal anaesthesia, has been found to be safe and effective when given in bolus i.v. doses to patients undergoing Caesarean section.[5]

The usual approach to the use of vasopressors in this clinical setting is reactive rather than proactive; spinal anaesthesia-induced maternal hypotension is allowed to develop and is then treated accordingly. Given the frequency with which it occurs, a more logical approach to its prevention may be the administration of pre-emptive vasopressors. Intramuscular (i.m.) ephedrine 37.5 mg has been found to be safe for the fetus; however, it is associated with a persistently high incidence of maternal hypotension.[6] The effect of ephedrine 45 mg i.m. has not been reported. No previous study has investigated the use of i.m.

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phenylephrine for the prevention of hypotension during spinal anaesthesia for Caesarean section, but it has been safely given via this route to healthy non-pregnant volunteers, including the elderly, in doses of 0.15 mg kg^{-1} (up to 10 mg).[7 8] In this randomized, double-blind, placebo-controlled study, we have evaluated phenylephrine 2 mg and 4 mg i.m., in comparison with ephedrine 45 mg i.m. and saline, given immediately after induction of spinal anaesthesia, in terms of haemodynamic stability, requirement for rescue i.v. vasopressor therapy and neonatal umbilical cord pH values.

Patients and methods

After obtaining hospital Ethics Committee approval and written informed consent, we studied 108 women, ASA status I or II, undergoing elective Caesarean section under spinal anaesthesia. Known hypertensive patients or those with a resting arterial pressure greater than 160/90 mm Hg were excluded from the study. The patients were randomized by a coded, opaque, sealed envelope technique into one of four groups: group 1 received phenylephrine 4 mg i.m. (P4), group 2 received phenylephrine 2 mg i.m. (P2), group 3 received ephedrine 45 mg i.m. (E45), while group 4, the control group (C), received saline 0.9%. All study medication was made up to 2 ml with 0.9% saline and administered by an anaesthetist not involved in the care of the patient or collection of data. A second anaesthetist, blind to the identity of the study medication, managed the patient.

Baseline non-invasive arterial pressure and heart rate readings were recorded at 1 min intervals by an automated non-invasive oscillometer (Criticon-Dinamapä) with data storage and printout facility, for 10 min before the start of the anaesthetic and continuing until surgery was completed. A 16-gauge i.v. cannula was sited in the non-dominant hand and 500 ml of Ringer's lactate solution given as a preload. Combined spinal–epidural anaesthesia (CSE) was instituted in the sitting position at L2–3 or L3–4, with a 26-gauge Sprotte spinal needle and 16-gauge Tuohy epidural needle, using a needle-through-needle technique. The i.m. injection of the study medication was given into the left vastus lateralis muscle immediately after the subarachnoid injection was completed. The time of i.m. injection was taken as time zero. The spinal injection contained 2.2 ml of 0.5% hyperbaric bupivacaine and fentanyl 20 mg, giving a total volume of 2.6 ml. The patient was then placed in the supine position, with a 15° left lateral tilt, after positioning of the epidural catheter to a depth of 3–4 cm in the epidural space. Block height was assessed with ethyl chloride spray at 5 and 15 min. Rescue i.v. bolus doses of ephedrine 6 mg were given if the patient became hypotensive or reported nausea, vomiting or dizziness. Hypotension was defined as a 25% decrease in mean arterial pressure (MAP) from baseline, which was taken as the lowest MAP recorded in the 10 min before receiving the study medication. (The lowest MAP value was chosen to minimize the influence of anxiety in patients with high initial MAP values.) The percentage change in MAP was calculated from the difference between baseline and the lowest recorded MAP, which occurred within the study period. The baseline heart rate was taken as the highest recorded heart rate before administration of the study drug. A printout of the haemodynamic data was obtained at the end of the operation. Neonatal Apgar scores at 1 and 5 min, and umbilical cord venous blood pH at delivery were also recorded. Top-ups for analgesia were not given via the epidural component of the CSE until the recording of data had been completed.

The number of patients required for enrolment in the study was calculated prospectively by assuming an incidence of hypotension of 80% in the untreated control group. We took a 35% reduction in the incidence of hypotension as being clinically significant. Therefore, taking α=0.05 and β=0.2, n=27 patients were required in each group to demonstrate these differences. Haemodynamic data, timing and dose of ephedrine required, together with physical characteristics were compared using analysis of variance with Dunnet's post-hoc test for difference between the groups compared with control. Interval data (parity, dermatomal sensory levels, Apgar scores) were compared using the Kruskal-Wallis test. Categorical data (incidence of hypotension and incidence of use of rescue i.v. ephedrine therapy) were compared after constructing contingency tables and applying the chi-squared test or Fischer's exact test as appropriate. Data were analysed using GraphPad Prism™ 2.0 on a personal computer running Microsoft Windows 98. A value of P<0.05 was considered statistically significant.

Results

All patients completed the study. Physical characteristics, baseline haemodynamic data and dermatomal sensory levels are given in Table 1. All groups were similar in terms of age, weight, parity, baseline haemodynamic data and dermatomal sensory levels. All the patients had adequate surgical anaesthesia. The incidence of hypotension is shown in Table 2. The incidence of hypotension was 33% in the phenylephrine 4 mg group, 48% in the ephedrine 45 mg group and 70% in the phenylephrine 2 mg group and control group. The incidence of hypotension was significantly lower in the phenylephrine 4 mg compared with controls (P=0.03). No patient in any group developed hypertension (MAP >25% increase from baseline) after the study medication. Figure 1 shows the percentage decrease in MAP. Patients who received phenylephrine 4 mg i.m. and ephedrine 45 mg i.m. had a significantly lower percentage reduction in MAP compared with controls and phenylephrine 2 mg i.m. (P=0.04). These two groups also required significantly lower doses of rescue i.v. ephedrine (P=0.02, Table 2). Patients in the phenylephrine 2 mg group required less rescue i.v. ephedrine than the control group, but this did not reach statistical significance (P=0.1). The incidence of

Table 1 Patient characteristics, haemodynamic data and dermatomal sensory levels. Age, weight, MAP and heart rate are expressed as mean (SD). Parity and block height are expressed as median (interquartile range). There was no significant difference between the groups. MAP=mean arterial pressure; T=thoracic dermatome; P4=phenylephrine 4 mg; P2=phenylephrine 2 mg; E45=ephedrine 45 mg

	P4 group *n*=27	P2 group *n*=27	E45 group *n*=27	Control *n*=27
Age (yr)	30.1 (18–41)	31.3 (22–38)	30.0 (22–37)	30.7
Weight (kg)	81.5 (11.4)	79.8 (11.3)	74.8 (13.1)	76.8 (15.1)
Parity	1.0 (0–2)	1.0 (0–2)	1.0 (0–1)	2.0 (1–2)
Baseline MAP (mm Hg)	81.5 (9.3)	88.1 (13.3)	81.5 (10.5)	86.0 (12.1)
Baseline heart rate	100.8 (14.8)	102.6 (15.9)	102.0 (15.4)	103.3 (13.1)
Block height (5 min)	T8 (T6–10)	T7 (T5–8)	T6 (T4–8)	T8 (6–10)
Block height (15 min)	T4 (T2–4)	T3 (T3–4)	T4 (T3–5)	T3 (T3–4)

Table 2 Incidence of hypotension and requirement for rescue i.v. ephedrine, with dose and time to first administration. Requirement of rescue i.v. ephedrine, with dose and time to first administration are expressed as mean (SD). Incidence of hypotension is expressed as number (%). *n*=27 in each group. **P*=0.02 for P4 and E45 compared with controls. ***P*=0.03 for P4 compared with controls. P4=phenylephrine 4 mg; P2=phenylephrine 2 mg; E45=ephedrine 45 mg

	P4 group	P2 group	E45 group	Control
Incidence of ephedrine requirement	21 (77%)	22 (81%)	21 (77%)	23 (85%)
Dose of rescue i.v. ephedrine (mg)	15.7 (15.7)*	17.9 (15)	15.8 (15.6)*	28.8 (20.6)
Incidence of hypotension	9 (33%)**	18 (70%)	13 (48%)	18 (70%)
Time to first ephedrine (min)	8.7 (7.6)	6.3 (4.7)	6.4 (6.1)	7.5 (4.8)

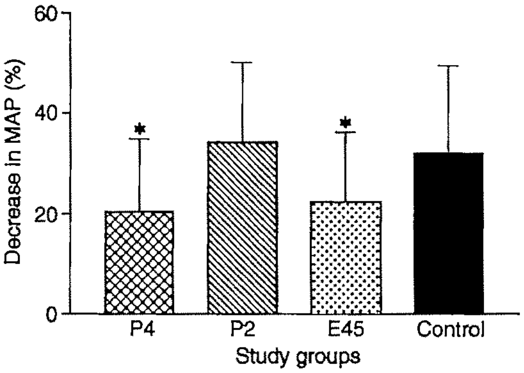

Fig 1 Percentage decrease in MAP from baseline. Values are mean (SD). **P*<0.05 in the P4 and E45 groups *versus* control. P4=phenylephrine 4 mg; P2=phenylephrine 2 mg; E45=ephedrine 45 mg; C=control; MAP=mean arterial pressure.

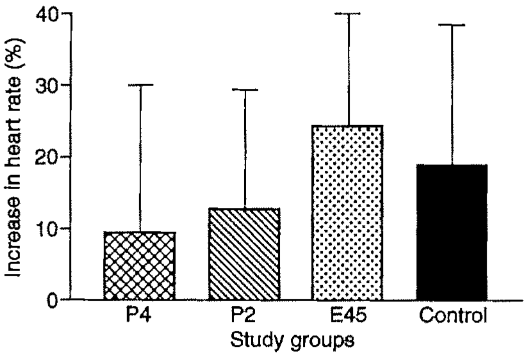

Fig 2 Percentage increase in heart rate. Values are mean (SD). There was no significant difference between the groups. P4=phenylephrine 4 mg; P2=phenylephrine 2 mg; E45=ephedrine 45 mg; C=control.

Table 3 Neonatal data. Cord pH is expressed as mean (SD) and Apgar scores as median (range). There was no significant difference between the groups. P4=phenylephrine 4 mg; P2=phenylephrine 2 mg; E45=ephedrine 45 mg

	P4 group	P2 group	E45 group	Control
Cord pH	7.31 (0.06)	7.31 (0.04)	7.29 (0.08)	7.28 (0.09)
Apgar score (1 min)	9 (9–9)	9 (8–9)	9 (9–10)	9 (9–9)
Apgar score (5 min)	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–10)

patients requiring rescue i.v. ephedrine was high in all groups (77–85%), but was not different between the groups. The time to first requirement for rescue i.v. ephedrine therapy was also similar between the groups (Table 2). There was no significant difference between the groups with respect to umbilical cord venous blood pH and Apgar scores (Table 3). The percentage change in heart rate (Fig. 2) did not show any significant difference between the groups. No patient developed bradycardia (heart rate <60 beats min^{-1}).

Discussion

This is the first report to our knowledge to show that phenylephrine 4 mg i.m. and ephedrine 45 mg i.m., given pre-emptively at induction of spinal anaesthesia for Caesarean section, reduce the severity of hypotension and the total dose of rescue i.v. ephedrine required compared with controls or phenylephrine 2 mg i.m. However, the incidence of the use of rescue i.v. ephedrine was not significantly different between the groups.

The prevention and treatment of maternal hypotension associated with spinal anaesthesia for Caesarean section remains a difficult problem, with no consensus as to the optimal mode of management. Hypotension is defined arbitrarily in most studies, with values ranging from a 20–30% reduction from baseline systolic arterial pressures (SAP) to absolute values less than 90–100 mm Hg.[1 3 6] The incidence of hypotension clearly depends on its definition and on the trigger for rescue ephedrine use. The trigger for rescue i.v. ephedrine use in our study was not only a 25% reduction in MAP, but also the presence of nausea, vomiting or dizziness which is the standard practice in our institution. Hence, we observed a high incidence of requirement for some rescue i.v. ephedrine therapy in all groups. However, our data demonstrated a reduction both in the severity of hypotension (in terms of percentage decrease in MAP) and the total dose of rescue i.v. ephedrine given. We chose the lowest MAP value in the 10-min stabilization period to allow anxious patients to settle and avoid spuriously high MAP values, which might have influenced the baseline measurement.

Measurement of SAP and MAP using non-invasive automated oscillometry has been found to be a valid method for non-invasive measurement of arterial pressure.[9] We chose MAP rather than SAP, as this is the component of arterial pressure that is most accurately determined by this method. Continuous invasive arterial pressure measurement is a more sensitive method of detecting hypotension, but is not usually indicated in a healthy population and would not be used in routine obstetric anaesthesia practice. In this study, we investigated the effect of i.m. vasopressors, given before the onset of hypotension, and found a therapeutically useful effect. We did not measure the effect of these agents on CO and derived systemic vascular resistance index (SVRI). However, this has been done in other studies.[4 10 11] Phenylephrine effectively restores SAP, MAP and diastolic arterial pressure, but decreases heart rate and CO when given by infusion to patients undergoing elective surgery under spinal anaesthesia.[10] Another study found a 58% incidence of bradycardia (heart rate <60 beats min^{-1}) when phenylephrine was given as an i.v. bolus after the induction of spinal anaesthesia.[5] None of the patients in the present study developed bradycardia. This may have been because of the overriding chronotropic effect of ephedrine when it was given as a rescue vasopressor. Alternatively, the absence of bradycardia may have been because of a baroreceptor-mediated reflex tachycardia in response to the reduction in systemic vascular resistance after the induction of spinal anaesthesia. Metaraminol, another α-agonist, has also been shown to be effective in restoring SAP and SVRI within 10–15 min, when given by continuous infusion in an elderly population.[11] Ephedrine is not a potent arterial vasoconstrictor; it maintains SAP mainly by increases in CO and heart rate.[4] All groups showed an increase in heart rate. As expected, the greatest increase was in the group receiving ephedrine 45 mg (Fig. 2), which can be explained by its β_1-adrenoreceptor activity.

The place of i.v. vasopressors for treatment of hypotension during Caesarean section is well established.[5 12 13] However, giving i.m. vasopressors before a spinal anaesthetic is more controversial because of concerns about reactive hypertension and adequacy of placental perfusion if the subarachnoid block fails.[14] We justified delaying the administration of i.m. vasopressors until the induction of spinal anaesthesia because of these concerns. A study comparing ephedrine 37.5 mg i.m., with placebo showed improved cardiovascular stability in the ephedrine group, but with a persistent 50% incidence of hypotension.[6] Sternlo and colleagues found ephedrine 0.6 mg kg^{-1} i.m., was effective in reducing the incidence of hypotension in patients undergoing hip arthroplasty under spinal anesthesia.[15] In spite of the differing patient populations, this dose is consistent with the findings in our i.m. ephedrine 45 mg group. Although, we have shown a reduction in the severity of spinal anaesthesia-induced hypotension with i.m. vasopressor therapy, there is still a persistently high incidence of hypotension. Perhaps earlier vasopressor administration or a larger dose may have reduced this further.

The timing of i.m. drug administration to achieve optimum efficacy can be unpredictable. Pharmacokinetic studies have suggested that the peak effect of i.m. phenylephrine or ephedrine is 10–15 min after administration.[16] The onset of subarachnoid block in this study occurred simultaneously with administration of the i.m. vasopressors, yet despite this, significant reductions in MAP were observed within a few minutes of establishment of the block. Nonetheless, we have demonstrated a reduction in the severity of hypotension, but no difference in the time to first requirement for rescue i.v. ephedrine. This suggests that giving i.m. vasopressors immediately after the intrathecal injection is not too late to achieve a beneficial effect. In addition, no hypertension was observed 30 min after i.m. vasopressor administration, when a peak vasopressor effect might have been expected, because of the continuing influence of spinal anaesthesia.

There was no impact on the fetus of any of our vasopressor therapy regimes in terms of umbilical cord venous blood pH and Apgar scores, but we did not undertake neurobehavioural studies.

In conclusion, we have shown that phenylephrine 4 mg i.m., and ephedrine 45 mg i.m., reduce the severity of hypotension and the total dose of rescue i.v. ephedrine therapy during spinal anaesthesia for Caesarean section. Further studies are warranted to determine the optimum dosage and timing of i.m. phenylephrine and ephedrine in terms of efficacy and safety before they can be recommended for routine clinical use in obstetric anaesthesia.

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I.V. ketoprofen for analgesia after tonsillectomy: comparison of pre- and post-operative administration

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We have evaluated the safety and efficacy of ketoprofen during tonsillectomy in 106 adults receiving standardized anaesthesia. Forty-one patients received ketoprofen 0.5 mg kg^{-1} at induction ('pre' ketoprofen group) and 40 patients after surgery ('post' ketoprofen group), in both cases followed by a continuous ketoprofen infusion of 3 mg kg^{-1} over 24 h; 25 patients received normal saline (placebo group). Oxycodone was used for rescue analgesia. Patients in the ketoprofen groups experienced less pain than those in the placebo group. There was no difference between the study groups in the proportion of patients who were given oxycodone during the first 4 h after surgery. However, during the next 20 h, significantly more patients in the placebo group (96%) received oxycodone compared with patients in the 'pre' ketoprofen group (66%) and the 'post' ketoprofen group (55%) (P=0.002). Patients in the placebo group received significantly more oxycodone doses than patients in the two ketoprofen groups (P=0.001). Two patients (5%) in the 'pre' ketoprofen group and one (3%) in the 'post' ketoprofen group had post-operative bleeding between 4 and 14 h. All three patients required electrocautery.

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Tonsillectomy (with or without adenoidectomy) is the most frequently performed throat surgery in adults. Although generally safe, it is associated with some complications including severe pain, bleeding, protracted vomiting and subsequent dehydration.[1–3] Analgesia after tonsillectomy is often inadequate. The side-effects of opioids, such as emesis, excessive sedation and risk of respiratory depression, can inhibit their use.

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent analgesics and can reduce or even eliminate the need for post-operative opioids.[4] However, they may also cause adverse effects, such as gastric irritation or renal dysfunction. It is also well known that NSAIDs prolong the bleeding time by inhibiting the biosynthesis of thromboxane A_2 and can increase blood loss during and after surgery even in healthy patients.[5]

Ketoprofen, a phenylpropionic acid derivative, has been in clinical use since 1973.[6] It is a widely used analgesic in many countries and has a good safety and efficacy record. A previous study demonstrated the efficacy of ketoprofen after tonsillectomy,[7] but further evaluation of the optimal time of administration and safety of ketoprofen is needed.

The aim of the present study was to evaluate the safety and efficacy of ketoprofen during tonsillectomy. We compared administration of the same dose of ketoprofen, before incision and after surgery, with a placebo group. The main study variables were pain at rest and during swallowing, need for rescue analgesic and the amount of perioperative bleeding.

Materials and methods

This prospective, randomized, double-blind, double-dummy and placebo-controlled study with parallel groups was approved by our Ethics Committee and conducted in accordance with the latest revision of the Declaration of Helsinki. All patients were informed and provided written consent. Patients with a history of severe adverse reactions to NSAIDs, bronchial asthma, kidney or liver dysfunction or bleeding disorders were excluded.

One hundred and six ASA I adult patients undergoing elective tonsillectomy or adenotonsillectomy were studied. Patients were allocated randomly to one of two ketoprofen groups or a placebo group. The allocation was computer

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generated and a sealed envelope method was used to ensure blinding. Forty-one patients received ketoprofen at induction ('pre' ketoprofen group) and 40 patients after surgery ('post' ketoprofen group); 25 patients received normal saline (placebo group).

A standardized anaesthetic technique was used. Each patient was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 15 mg, 60 min before induction of anaesthesia. Fentanyl 2 μg kg^{-1} was given intravenously and anaesthesia was induced with thiopental 5 mg kg^{-1}. Neuromuscular blockade was achieved with *cis*-atracurium 0.1 mg kg^{-1}. Anaesthesia was maintained with 2–3% sevoflurane (inspired concentration) in 65% nitrous oxide in oxygen with intermittent positive pressure ventilation. On completion of surgery, neuromuscular blockade was reversed with neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1}. For intraoperative fluid maintenance, all patients were given 0.9% saline 10 ml kg^{-1} h^{-1} and, after surgery, 5% glucose in 0.3% saline 2 ml kg^{-1} h^{-1} until able to tolerate fluids by mouth.

In the 'pre' ketoprofen group, patients were given ketoprofen 0.5 mg kg^{-1} (Ketorin; Orion, Espoo, Finland) intravenously, mixed with 10 ml of normal saline and injected over 5 min after induction of anaesthesia but before surgical incision, and placebo (10 ml normal saline) injected over 5 min in the postanaesthesia care unit (PACU) followed by a continuous i.v. ketoprofen infusion of 3 mg kg^{-1} over 24 h. In the 'post' ketoprofen group, patients were given placebo (10 ml normal saline) after induction, and ketoprofen 0.5 mg kg^{-1} i.v. in the PACU followed by a ketoprofen infusion of 3 mg kg^{-1} over 24 h. In the placebo group, patients were given normal saline after induction and, in the PACU, normal saline infusion. The drug syringes were prepared by a nurse not otherwise involved in the study, ensuring blinding.

All tonsillectomies were performed between 11 a.m. and 2 p.m. by six surgeons with previous experience of over 50 procedures using an electrodissection technique. Blood loss was assessed by visual estimation of blood volume in sponges and the suction bottle. A study nurse recorded the length of surgery.

Pain intensity after surgery was assessed by asking patients to express their pain on a 100 mm visual analogue scale (VAS; 0=no pain, 100=worst possible pain). Pain scores were recorded at rest and on swallowing 1, 2, 3 and 4 h after surgery in the PACU. Thereafter, on the ward, pain scores were recorded at 8 p.m. and 8 a.m., and just before discharge. At discharge, patients were also asked to rate their worst pain and the average level of pain they had experienced on the ward.

Rescue analgesic medication consisted of oxycodone 0.05 mg kg^{-1} i.v. during the first 4 h after surgery (in the PACU) and thereafter 0.1 mg kg^{-1} i.m. (on the ward). Rescue analgesic was given if the pain score at rest was ⩾30. The oxycodone dose was repeated at 15–30 min intervals until the pain had diminished to slight (pain score at rest <30). All rescue analgesic doses were recorded. No other analgesic medication was permitted during the study. Time to the first voiding, nausea and vomiting and all adverse effects were recorded for each patient. Bleeding was classified as minor if medical attention was required and intravenous fluid or suction of the clot was initiated, and major if electrocautery or reoperation was required.

Patients were discharged 24–30 h after surgery when they had no or mild pain, were able to tolerate clear fluids and soft food, had no bleeding and had no nausea or vomiting. On discharge, all patients received a ketoprofen capsule (2 mg kg^{-1}). For post-operative pain relief at home, all patients were given ketoprofen 50 or 100 mg capsules (Ketorin) and were instructed to take two or three capsules over 24 h (3–5 mg kg^{-1} day^{-1}) for 5–10 days. For rescue analgesia at home patients were prescribed Panacod tablets (Sanofi-Winthrop, Solna, Sweden) containing, per tablet, 500 mg paracetamol and 30 mg codeine.

The sample size was based on detecting a difference of ⩾35% in the need for rescue analgesia between the 'pre' and 'post' ketoprofen groups at a 0.05 significance level with 80% power.

Statistical analysis of continuous variables was performed using the Kruskal–Wallis test. The Mann–Whitney test with Bonferonni correction was used for *post hoc* analysis. The χ^2 test was used for categorical variables. Correlation between independent variables was tested with the Pearson correlation coefficient. Differences were considered statistically significant when the *P* value was <0.05. Results are presented as number of cases (%), mean (SD) with 10th and 90th percentiles, correlation coefficient (*R*) or mean difference (95% confidence intervals (CI)) as appropriate.

Results

Patient characteristics are shown in Table 1. No protocol violations likely to interfere with the study variables were recorded. No patients were withdrawn from the study.

Ketoprofen administration before incision did not increase the amount of blood loss or the duration of surgery and there was no difference between the three study groups in these two variables. However, in the whole study population the amount of intraoperative blood loss correlated positively with the duration of surgery (*R*=0.45, *P*=0.001) (Table 1).

Thirty-four patients (83%) in the 'pre' ketoprofen group, 34 (85%) in the 'post' ketoprofen group and all 25 in the placebo group received rescue analgesia. There was no difference between the study groups with respect to the proportion of patients receiving oxycodone in the PACU. During the next 20 h, significantly more patients in the placebo group (24 patients (96%)) received oxycodone compared with the 'pre' ketoprofen group (27 patients (66%)) (difference 30%, 95% CI: 14–47%) and with the

Table 1 Patients and surgery characteristics: mean (SD) with 10th/90th percentiles or the number of patients. There were no significant differences between study groups.

	'Pre' ketoprofen group (n=41)	**'Post' ketoprofen group (n=40)**	**Placebo group (n=25)**
Sex (male/female)	17/24	20/20	12/13
Age (yr)	31 (17–59)	29 (17–56)	29 (17–57)
	17–49	18–43	17–51
Height (cm)	172 (9)	173 (9)	172 (11)
	160–186	160–186	158–186
Weight (kg)	72 (14)	74 (15)	70 (14)
	55–92	57–97	53–90
Duration of surgery (min)	24 (15)	23 (13)	24 (9)
	10–50	10–37	15–37
Blood loss (ml)	22 (26)	30 (40)	42 (41)
	2–58	1–100	3–100

Table 2 Number of oxycodone doses during the first 24 h after surgery: mean (SD). *Significantly different from 'pre' ketoprofen (P=0.03) and post-ketoprofen (P=0.036). **Significantly different (P<0.01) from 'pre' ketoprofen and post-ketoprofen (Mann–Whitney test with Bonferroni correction)

	'Pre' ketoprofen (n=41)	**'Post' ketoprofen (n=40)**	**Placebo (n=25)**
Early: 0–4 h	1.5 (1.2)	1.5 (1.4)	2.7 (2.0)*
Late: 5–24 h	1.5 (1.8)	1.5 (2.0)	2.9 (1.7)**
Total	3.0 (2.5)	3.1 (2.9)	5.6 (1.7)**

'post' ketoprofen group (22 patients (55%)) (difference 41%, 95% CI: 24–58%) (P=0.002).

There was no statistically significant difference between the two ketoprofen groups with respect to the mean dose of rescue analgesia, but patients in the placebo group received significantly more oxycodone doses than patients in the two ketoprofen groups (P=0.001). The mean difference between the placebo group and the other two groups was the same ('pre' ketoprofen group, 2.6 (95% CI: 1.3–3.9) doses; 'post' ketoprofen group, 2.6 (95% CI: 1.1–4.0) doses) (Table 2).

Patients in the two ketoprofen groups experienced less pain than those in the placebo group (Figure 1). The occurrence of insufficient pain relief (defined as a VAS score of >30 mm at rest and >50 mm on swallowing) was significantly more common in patients receiving placebo than in those receiving ketoprofen (P=0.001) (Figure 2). The worst pain at rest and on swallowing was less in both ketoprofen groups than in the placebo group (P<0.03). A similar difference was observed in mean pain scores (Figure 3).

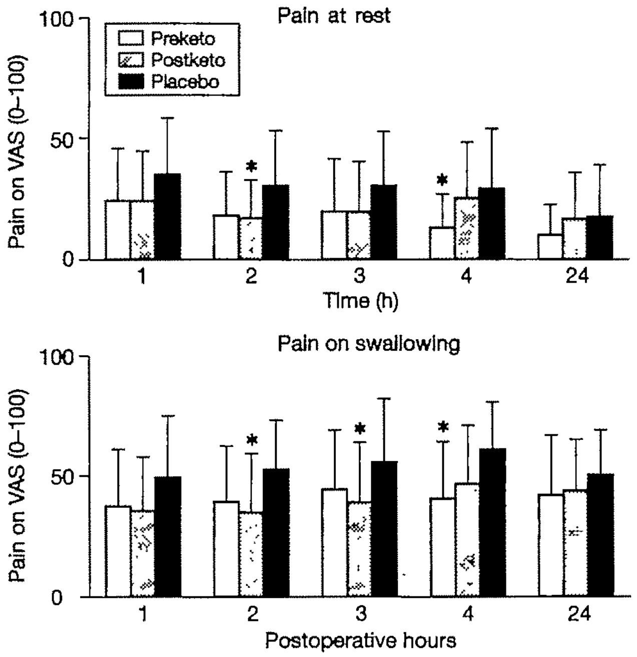

Fig 1 Mean (SD) VAS pain scores at rest and on swallowing for the study groups at various times after surgery. *Placebo group significantly different (P<0.05) from both ketoprofen groups (Mann–Whitney test with Bonferroni correction).

There was no difference between the study groups in the time to first voiding after surgery (data not shown). Thirty-seven patients (35%) developed adverse effects, none of which were serious. The incidence was similar in the three groups (Table 3). Clinically significant bleeding occurred in two patients (5%) in the 'pre' ketoprofen group, one (3%) in the 'post' ketoprofen group, and none in the placebo group. All three patients needed electrocautery under local anaesthesia to stop bleeding. Bleeding was observed 4 and 8 h after surgery in the 'pre' ketoprofen group and 14 h after surgery in

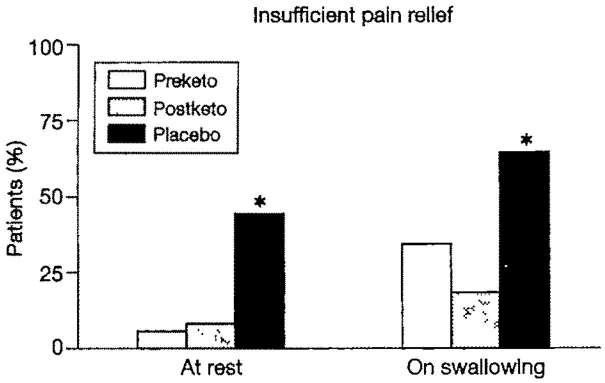

Fig 2 The proportion of patients with insufficient pain relief, defined as a VAS pain score >30 mm at rest and >50 mm on swallowing, in the study groups. *Placebo group significantly different (P=0.001) from both ketoprofen groups (χ^2 test).

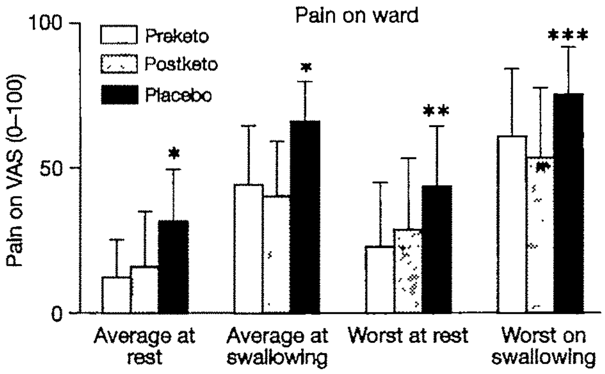

Fig 3 Mean (SD) VAS pain scores for average and worst pain at rest and on swallowing on ward during the first 24 h after surgery in the study groups. *Placebo group significantly different (P=0.001) from both ketoprofen groups; **placebo group significantly different from 'pre' ketoprofen group (P=0.001) and 'post' ketoprofen group (P=0.03); ***placebo group significantly different from 'pre' ketoprofen group (P=0.02) and 'post' ketoprofen group (P=0.001) (Mann–Whitney test with Bonferroni correction).

the 'post' ketoprofen group. No blood transfusions were required.

Discussion

In this study, ketoprofen was associated with an opioid sparing effect and patients receiving it were in less pain, as shown by others.[7] However, no pre-emptive effect was found: recovery was similar when ketoprofen was administered before or after surgery.

Pre-emptive or proactive administration of NSAIDs is justified because of the delayed action of these drugs. However, in this study, ketoprofen administered after surgery performed as well as the same dose administered before incision. This is consistent with assumptions that, in addition to its peripheral action, ketoprofen has a rapid central analgesic action.[8]

Table 3 Adverse effects after tonsillectomy in the study groups (number (%))

	'Pre' ketoprofen (n=41)	**'Post' ketoprofen (n=40)**	**Placebo (n=25)**
Vomiting			
Early: 0–4 h	3 (7%)	1 (3%)	1 (4%)
Late: 5–24 h	11 (27%)	7 (18%)	5 (20%)
Recurrent: ≥3 episodes	2 (5%)	2 (5%)	1 (4%)
Total	12 (29%)	7 (18%)	5 (20%)
Nausea without vomiting	3 (7%)	5 (13%)	2 (8%)
Headache	–	–	1 (4%)
Pruritus	1 (2%)	–	–
Excessively sedated	–	–	2 (8%)
Patients with one or more adverse effects	15 (37%)	13 (33%)	9 (36%)

NSAIDs increase bleeding time but usually within normal limits.[9] The reduction in thromboxane A_2 biosynthesis produced by NSAIDs prevents platelet aggregation and therefore inhibits haemostasis. Whether or not the increase in blood loss during surgery is clinically significant is controversial. Ketoprofen has been used successfully in children undergoing adenoidectomy without any major peri-operative bleeding.[10] The safety of ketoprofen during throat surgery may be supported by the present study, as no significant differences were found between the study groups in the amount of peri-operative bleeding. Post-tonsillectomy haemorrhage continues to pose serious problems. Over the years, the incidence of significant bleeding has decreased, but it still occurs in approximately 2–3% of patients.[11–16] In contrast to two recent studies where peri-operative use of ketoprofen did not cause post-operative bleeding,[7 17] three cases of haemorrhage occurred 4–14 h after surgery in our study. Most studies have investigated small numbers of patients, introducing a large risk of type II error. However, some conclusions may be drawn. (i) Studies suggest that the risk of bleeding varies between different NSAIDS. In many studies, ketorolac has been associated with a higher incidence of bleeding than propionic acid derivatives (ibuprofen, naproxen or ketoprofen).[7 10 15 18–25] (ii) Post-tonsillectomy bleeding seems to occur with a similar incidence when paracetamol (with or without codeine) is used instead of propionic acid derivatives.[20 26–31] (iii) When opioids are used alone, bleeding still occurs.[7 21–24] Moreover, when opioids are used without background analgesia, post-operative nausea and vomiting are common. This may delay discharge.[24 29] (iv) Nerve blocks and periotonsillar infiltrations with local anaesthetics have not improved anaesthesia after tonsillectomy and studies have shown that post-operative bleeding occurs as often as with other analgesic techniques.[27 28 31] (v) Unlike Stoeckli and colleagues,[32] we supposed that fibrin glue did not decrease post-operative pain and bleeding.

Vomiting is common after tonsillectomy and may be induced not only by swallowed blood and oropharyngeal irritation but also by opioids.[7 33] We did not find any difference between the groups with respect to the incidence of vomiting, but overall it was less than reported previously.[33] Opioids may have different emetic properties. We have found that fentanyl induces less vomiting than morphine.[34] The present study suggests that oxycodone is also associated with a fairly low incidence of vomiting, as only 23% of our patients vomited, compared with 41% in a previous study.[33]

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Analysis of the French health ministry's national register of incidents involving medical devices in anaesthesia and intensive care

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This study details all incidents involving medical devices used in anaesthesia and intensive care reported to the relevant authorities in France in 1998. There were 1004 reports during that year. Incidents were classified as serious (harmful to patients) in 11% of cases; death resulted in 2% of cases. Equipment for ventilation and infusion, and monitors of all kinds, accounted for most of the reports, representing 37%, 30% and 12%, respectively, of all reports. The leading causes of failure varied according to the category of device. User errors, quality control problems during production of the device and design faults were the three main causes. The problems identified during the study period enabled the faulty medical devices to be improved in 12–44% of cases. We conclude that post-marketing vigilance is a useful way of improving the quality of medical devices.

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Most accidents in anaesthesia are caused by human error,[1 2] but medical devices may also fail and do cause critical incidents. Such events have appeared in the medical literature since the earliest days of case reports, but most are anecdotal.[3] The traditional approach in this field has been to collect incident reports in a single clinical setting, e.g. ICU or anaesthesia, and to list all the clinical mishaps that have occurred in a certain period. The aim has been to assess mishaps as a whole. Pioneering studies by Cooper, Newbower and Kitz used closed-claims analysis to track a large series of incidents.[4] An Australian prospective analysis of 2000 incidents in anaesthesia represents another interesting approach.[5 6] However, of all the factors studied, devices have been involved only marginally, and very few series have focused on them.[4,7] Post-marketing surveillance and reporting systems have opened a new era in the collection of device-related mishaps. Incident reporting managed by the United States Federal Drug Administration (FDA) started in 1974. Under European Community regulations, many European countries also now have this kind of reporting. The principle has been applied by law in France since 1996,[8] and details have been published.[9 10] Under this decree, anyone who is aware of an incident in which a patient has been or may have been injured must notify the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS). The reporting of less serious incidents involving medical devices is also being encouraged. Despite the extension of post-marketing surveillance and reporting to all European countries, no data have yet been published. We aim to begin this process by describing key findings extracted from the French national database of 1998 post-marketing reports in anaesthesia and intensive care.

Materials and methods

We have analysed all the incident reports in anaesthesia and intensive care medicine which were sent to and processed by the French authorities in 1998. These reports concerned medical devices that had failed or which injured or may have injured patients. As the launch of the post-marketing

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Table 1 Incidents by category of medical device (MD). *% of declarations for each class of MD; regional=regional anaesthesia; rewarming=devices used to warm patients or perfusion fluids

Type of MD *n* **(% of total)**	**Reported as severe** *n* **(%*)**	**Judged severe (no death)** *n* **(%*)**	**Reported as not severe** *n* **(%*)**	**Deaths** *n* **(%*)**
Regional 10 (1.0)	4 (40)	2 (20)	4 (40)	0 (0)
Catheter ports 82 (8.1)	52 (63)	30 (37)	0 (0)	0 (0)
Defibrillators 27 (2.7)	6 (22)	4 (14)	17 (64)	0 (0)
Medical gases 49 (4.9)	18 (37)	2 (4)	28 (57)	1 (2)
Incubators 25 (2.5)	12 (48)	7 (28)	6 (24)	0 (0)
Monitors 122 (12.1)	41 (34)	9 (7)	64 (52)	8 (7)
Infusion 309 (30.7)	42 (14)	23 (7)	238 (77)	6 (2)
Rewarming 8 (0.8)	0 (0)	4 (50)	4 (50)	0 (0)
Ventilation 372 (36.9)	123 (33)	27 (7)	217 (59)	5 (1)
Total of columns 1004 (100)	299 (30)	111 (11)	578 (57)	20 (2)

process was still relatively recent in France, voluntary reports of less severe incidents were also encouraged. Incident reports were sent by public and private hospitals and by health organizations from other European countries. Although manufacturers are required by European regulation and by their quality assurance policy to notify problems with their products, few such notifications were received. Each report was set out on a pre-printed form designed by the French authorities. This listed the type of device, a short description of the incident and the name of the reporting institution. Whenever it was judged necessary, the authorities contacted the institution submitting the report for additional details and prompted the manufacturer to examine the device. In complex cases, a clinical or bioengineering expert visited the centre to see the device and review the facts with those who had made the original report. In a very few cases, an independent laboratory was asked to examine the device.

Results

We analysed the 1004 reports listed in the database in 1998. At the time we examined them, all reports had been finalized. The reports were divided into nine categories (Table 1). 'Regional' anaesthesia refers to all single-use needles and catheters used in this kind of anaesthesia. 'Catheter ports' refers to the type of implanted device (including a chamber and a catheter) mostly used for the perfusion of cytotoxic drugs. In France, these devices belong to the field of intensive care. The 'infusion' category includes catheters (46%), syringes and tubing (10%), syringe pumps (23%) and all other forms of needles, syringes, filters and other single-use equipment (21%). The 'defibrillator' category includes paddles, battery chargers and other electrical supplies. 'Medical gas delivery' refers to delivery systems for oxygen, nitrous oxide, air and vacuum (from the tank through to the wall of the room where the gas is used). 'Incubators' are those in neonatal intensive care. The 'monitors' category includes all kinds of device used in intensive care or the operating theatre whether compact (19%) or modular (55%), accessories such as Sp_{O_2} sensors (8%) and all other kinds of monitor (18%). The 'rewarming devices' category includes those used to rewarm patients (excluding incubators) or infusion fluids. It also includes pumps used to accelerate transfusion. 'Ventilation' refers to equipment used to provide supplemental oxygen or to ventilate patients' lungs, including masks, tracheal tubes (25%), ventilators of any type (51%) and attached components, e.g. unidirectional valves (4%), circuits (6%), volatile anaesthetic vaporizers (2%), gas mixers (3%) and accessories (9%).

About 30% of the incidents were reported by users to be severe (an incident which harmed or may have harmed the patient) (Table 1). However, after review by a member of the French authorities, only 11% retained this rating.

Twenty reports (2%) were associated with patient death. The failure of the device itself accounted for 12 accidents: two ventilators of the same type caused massive pneumothorax when they failed; this led to changes in the design of the apparatus. The devices involved in all the other cases of device failure were different in each case. In four cases the monitors did not sound an alarm in response to ventricular fibrillation or asystole. In two other cases, the monitors mistook the activity of a pacemaker for that of the heart, and produced no alarm even when the patient was already dead. Two cases of gas supply failure each killed one patient through contamination of the oxygen line with nitrous oxide. In two cases an isoflurane vaporizer gave an overdose, resulting in the death of one patient. Incorrect use was the second most common cause of death (n=7). One user failed to make proper use of an oxygen tank for home ventilation and died from anoxia. Another death was attributed to a heat and moisture exchanger (HME), which was attached to a one-way Ambu valve in the wrong direction; ventilation became impossible and the patient died from anoxia. This problem with one-way valves prompted an order from the French authorities for design changes to make such mistakes impossible. The four deaths involving infusion equipment were associated with catheter fracture and migration, cardiac tamponade and embolism, usually resulting from technical errors made during insertion of catheters. One patient died because all alarms had

Table 2 Nature of inquiry for each category of medical device. *% of declarations for each class of device; regional=regional anaesthesia; rewarming=devices used to warm patients or perfusion fluids

Type of device *n* **(% of total)**	**Expert evaluation done (%*)**	**Expert evaluation impossible (%*)**	**Expert evaluation deemed not necessary (%*)**
Regional 10 (1.0)	30	60	10
Catheter ports 82 (8.1)	40	60	0
Defibrillators 27 (2.7)	74	22	4
Medical gases 49 (4.9)	71	22	6
Incubators 25 (2.5)	64	32	4
Monitors 122 (12.1)	82	16	2
Infusion 309 (30.7)	24	75	0
Rewarming 8 (0.8)	75	25	0
Ventilation 372 (36.9)	52	44	4
Total 1004 (100)			

been turned off to make life more comfortable for the nursing staff. We encountered one death in which the device did not seem to be faulty. The clinician using a pulse oximeter failed to identify as 'false' a very low Sp_{O_2} value during extracorporeal circulation for repair of a congenital defect, although pulse oximetry is known to be unreliable in this context. However, this problem was not the main cause of death.

While 98% of the accidents were not fatal, several of them warrant further examination. Some of these cases involve the same problems as the fatal ones described above.

The rupture of epidural catheters in the epidural space was the most significant problem in regional anaesthesia. The most significant catheter port incident was catheter fracture (44% of reports for catheter ports), leading to their migration into the heart and pulmonary veins in 36% of cases.

Defibrillation equipment caused burns to patient or doctor in three cases (11%). A shock could not be delivered in four cases. Three cases were the result of incorrect use. For example, synchronization to the ECG requires a delay before the shock can be triggered and delivered. This function was not understood by the user, who thought the device had failed. Other problems included the unexpected failure of batteries or components. Checking procedures had often not been performed properly or at the correct time.

Incidents involving systems for medical gas delivery and gas analysers were mostly minor, such as leaks, simple failure of gas analysers or rotameter inaccuracies. However, serious errors involved the misconnection of medical gas lines; these occurred in four cases and were possibly caused by defects in the sockets. Still more seriously, there were four cases of ignition of aluminum oxygen pressure regulators after the oxygen high pressure valve, upstream of the regulator, was opened rapidly, causing major burns to users. Two non-fatal cases of contamination of the oxygen lines with nitrous oxide were noted.

For infusion equipment (excluding catheter ports) there were few severe accidents. These included the migration of catheters inside vessels, air embolism and infusion rate errors with syringe pumps. Minor problems were numerous and mainly caused by errors of use and/or failures of quality assurance during manufacture.

The extent of problems with monitors varied according to the type. Haemodynamic monitors (45%) headed the list, followed by Sp_{O_2} monitors, including their accessories (15%). Monitors failed mainly because of component breakdown and errors in design, including software (Table 3).

Several cases involved problems of ventilation. Unexpected failure without an alarm occurred with 23 ventilators, and barotrauma with seven. Disposable one-way valves were reversed when an HME filter was placed between the valve and Y-piece in three non-fatal cases. A tracheostomy tube migrated into one patient's trachea; this was caused by the connecting piece becoming detatched. Enquiries showed that the glue used in the production of these devices could melt when iodine and alcoholic solutions were used to clean the tracheostomy incision. Failures of tracheal tube securing devices were reported in five instances, allowing the tube to twist and reduce ventilation. A design fault seemed to be the cause in most cases.

The database was then analysed to assess the mode of investigation used, and the causes of failure, classified by category of equipment (Tables 2 and 3). Table 2 shows the number of reports that required a formal analysis of the faulty device by the manufacturer or an independent laboratory. Such a formal analysis was possible in only 40% of cases involving perfusion catheters, catheter ports and equipment for regional anaesthesia. This was because most users, having declared the problem, discarded the device, either by accident or on the grounds that it was 'contaminated with blood' and thus not safe to send to a laboratory. Thus, effective laboratory investigations were performed in fewer than 33% of cases. This was due to the large number of component breakdowns that were easily recognized without specific expertise.

The origin of the problem, whenever this could be identified, is described in Table 3. Incorrect use was a factor in >70% of the cases involving catheter ports and equipment for regional anaesthesia. Incubators were judged to be

Table 3 Problems identified, and cases where manufacturer modified the design of the medical device. Percentages do not always add up to 100% for each class of device. In some cases two causes were found; in others none was identified. *% of declarations for each class of device; regional=regional anaesthesia; rewarming=devices used to warm patients or perfusion fluids; †devices were declared obsolete according to French or European standards

	Origin of problem (%*)								
Type of device	**User error**	**Quality assurance**	**Design fault**	**Software defect**	**Component breakdown**	**Obsolete device†**	**Unavoidable problem**	**Maintenance problem**	**Modifications of device by manufacturer**
Regional	70	20	0	0	0	0	10	0	20
Catheter ports	71	5	0	0	0	0	0	0	0
Defibrillators	41	11	7	4	41	0	0	0	18
Medical gases	14	12	26	2	12	0	2	24	22
Incubators	40	0	16	0	4	20	0	16	44
Monitors	14	8	24	12	39	2	14	4	19
Infusion	37	22	11	2	4	4	6	5	15
Rewarming	50	12	0	0	12	12	0	0	12
Ventilation	16	22	17	2	27	1	5	5	19

obsolete, according to recent French norms, in 20% of cases. Maintenance was found to be a significant cause of failure only for medical gas supplies. Through quality assurance failures or design faults, including software, manufacturers could be judged responsible for the problems in 30–40% of cases. Simple component failure was more evenly distributed among the various categories of device.

Considering the whole database, it is clear that this post-marketing survey led to design changes in 12–44% of cases. These reports led the French health authorities to issue 11 directives demanding the withdrawal from the market or restricted use of the problematic devices. In almost all cases there was a design fault.

Discussion

The French national reporting system is very similar to those of other European countries[11] and North America.[12] Its object is to maintain patient safety. Devices are controlled by the ISO9000 series of quality system standards, which apply to manufacturers; these aim for high quality and safety throughout the life of the product from its design through to its use and maintenance. The incident reporting principle complements the ISO9000 system, as it allows users to report problems that might have escaped the manufacturer or which may appear after the release of the device on to the market. This study is the first comprehensive analysis of French post-marketing activity since it began in the field of anaesthesia and intensive care in 1996.

Vigilance is important in anaesthesia as failure of devices used in this field may place the patient at high risk.[13] Hart and colleagues[6] categorized 22% of incidents reported in ICUs as severe (this category included those in which patients died and other severe incidents). The duration of injuries was permanent or long-lasting in 6%. Equipment featured in 41% of cases. Gilron[14] in Canada noted that, although anaesthetic devices accounted for only 2.3% of newly marketed medical devices, they accounted for 8.6% of all problems and recalls and 37% of alerts. Similarly, anaesthesia accounted for 32% of all reports in France.

Infusion equipment and catheter ports

All the incidents we encountered in this field involved known problems. Errors during insertion and failure to check the catheter position radiologically accounted for the majority of problems with catheters. This led to vein perforation and to catheter rupture with migration and leaks. Catheter ports failed and migrated because of unnoticed 'pinch-offs'.[15 16] Like others, we found many errors in the use of infusion pumps.[17] This highlights the fact that further education and safety measures are required, even with simple and commonly used devices such as catheters and pumps.

Monitors

Monitors, especially pulse oximeters and capnometers, are important for detecting anaesthetic mishaps, so increasing their reliability is a key issue.[18 19] Short and colleagues[20] noted that, of the 125 critical incidents reported during a quality assurance programme, 50% were detected by the anesthetist and 34% by monitoring equipment. This highlights the potential risk posed by monitor failures, especially if there is no built-in alarm system.

Defibrillators

Defibrillator failure because of defective batteries is the major cause of failure in published reports.[21] The systematic use of checklists and tests has been advocated in response to incidents, especially for defibrillators that are seldom used. Errors of operation were also frequent, especially in devices linked to the patient's ECG. Users did not know how these differed in function from more classical devices. This highlights a need to educate users and to label the front panel clearly with instructions for fast, error-free operation.

Ventilation and medical gas supply

In most cases, problems arising from ventilation devices were caused by device failure or human error. There were two main problems with medical gas supply: (i) contamination of oxygen lines with nitrous oxide or air due to a valve failure[22–24] and (ii) ignition of oxygen flow regulators made of aluminium alloy, which can melt at a low temperature, causing serious burns to users. These devices are liable to blow their fuses, which may ignite any inflammable equipment. This has encouraged the French authorities to forbid the use and sale of regulators including parts made of aluminium.

Incubators

Several devices were not sufficiently protected against possible errors of use. Serious burns arose from errors in incubator settings, or in placing the temperature probe on the child. Another was caused by incorrectly placed surgical drapes directing a hot air stream towards the baby. This risk was mentioned in the user manual, but the manufacturers had not gone on to reinforce it with an alarm. A warning from health authorities, an information campaign and the addition of warning labels on the canopy did not prevent another accident of the same type from occurring a year later. This highlights the fact that manufacturers should consider how people actually use their devices in practice, e.g. performing surgical operations in closed incubators instead of open ones.

Human errors were very frequent: they involved 14–71% of the reports, depending on the category of the device. Most of these incidents were caused by negligence or inadequate knowledge, despite clear instruction manuals. It seems that medical device-orientated 'culture' is not sufficiently widespread and does not keep up with industrial progress. Williamson and colleagues[25] reported in the Australian Incident Monitoring Study that errors of judgement when using medical devices, a failure to check and technical errors represented 16%, 13% and 13% of human errors, respectively. Clayton[26] showed that 55% of residents were not able to check anaesthesia machines according to the standards of the New Zealand College of Anaesthetists and that only 16% of them could use defibrillators properly and solve problems involving this device. Reducing errors of this kind will require more education. For this reason, the German authorities have requested users to undergo specific training on each new medical device introduced in a clinical department before they use them on patients.

Another study identified a failure of regular checking in 33% of the reports.[21] This was taken up as a major regulatory issue by the French authorities, who require by law that all devices used in the operating theatre should be checked daily before use and according to formal checklists. This recommendation also imposes a 'between case' simplified check.[27]

We found incidents of equipment failure that differed from those reported by Webb and colleagues[5] Equipment failures represented only 9% of all incidents reported in their study. Ventilation equipment accounted for 44%. These were due to one-way valve failures in 43% of cases and to leaks of various kinds in 13%. The remaining causes were miscellaneous. Forty per cent of incidents involving ventilators were actually or potentially life-threatening. Monitors were involved in 24% of incidents, of which arterial pressure monitors accounted for 26%. All were described as potentially life-threatening. Oximeters, oxygen analysers, capnographs and pulse oximeters each accounted for about 20%. Surprisingly, infusion pumps accounted for fewer than 2% of all incidents. This pattern of incidents is strikingly different from ours. It may be that the types of event reported in the two studies differed. In the study of Webb and colleagues,[5] all consecutive events occurring during anaesthesia were reported, including malpractice and probably also numerous trivial problems resulting from human error. Under these circumstances, equipment failures were likely to be underestimated. Conversely, our data featured equipment failures specifically. However, both studies relied on voluntary reporting. This underestimates the true occurrence of incidents. For example, a study by Sandborn and colleagues[28] showed that only 4% of electronically detected incidents had led to a voluntary report. To exploit equipment failures in improving safety and reliability, and to further the education of users, incident reporting must become mandatory. Since ECRI (Emergency Care Research Institute, 19462-1298 Plymouth Meeting, Pennsylvania, USA) and a systematic survey and analysis of medical device failures was introduced in the USA, this reporting has been shown to be successful.[29]

We conclude that vigilance leads to a better understanding of the problems involving medical devices. The French experience is positive, and may help to improve safety.

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LABORATORY INVESTIGATIONS

Differential nitric oxide synthase activity, cofactor availability and cGMP accumulation in the central nervous system during anaesthesia

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We investigated the effects of anaesthesia on dynamic nitric oxide production, concentrations of tetrahydrobiopterin and the accumulation of cyclic GMP (cGMP) in the rat central nervous system (CNS). Rats were assigned to anaesthesia with halothane, isoflurane, pentobarbital, diazepam, ketamine or xenon (n=6 per group). After 30 min, [^{14}C]L-arginine (i.v.) was given and, after a further 60 min of anaesthesia, rats were killed and exposed immediately to focused microwave radiation. After removal of the brain and spinal cord, nitric oxide production from radiolabelled arginine (and hence nitric oxide synthase activity during anaesthesia) was measured as [^{14}C]L-citrulline by scintillation counting. cGMP was determined by enzyme immunoassay and tetrahydrobiopterin by fluorescence HPLC, in brain regions and the spinal cord. Nitric oxide synthase activity was similar in all brain regions but was lower in the spinal cord, and was unaffected by anaesthesia. cGMP was similar in all areas of the CNS and was significantly decreased in rats anaesthetized with halothane. Isoflurane produced similar effects. In contrast, ketamine and xenon anaesthesia increased cGMP in the spinal cord, brainstem and hippocampus. Diazepam and pentobarbital had no effect. Tetrahydrobiopterin concentrations were similar in all areas of the CNS and were increased in the cortex and hippocampus after anaesthesia. We have shown profound differential effects of anaesthesia on the nitric oxide pathway in the rat CNS.

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Nitric oxide is synthesized from L-arginine by the action of nitric oxide synthase (NOS), and type I or neuronal NOS is the predominant isoform of the enzyme within the central nervous system (CNS).[1] All NOS enzymes have a requirement for tetrahydrobiopterin for catalytic activity, and NOS activity is governed by tetrahydrobiopterin availability.[2] The primary way in which nitric oxide mediates cellular and intercellular communication is through the activation of soluble guanylyl cyclase, resulting in cGMP formation and the regulation of neuronal ion channels. Nitric oxide is a component of the excitatory and inhibitory neurotransmitter pathways involved in anaesthesia,[3] and anaesthetics have been shown to alter aspects of the nitric oxide pathway, including cGMP accumulation, metabolites of nitric oxide and NOS activity,[3–6] although some data are conflicting.

It has generally been assumed that changes in cGMP entirely represent nitric oxide-dependent changes, and levels of cGMP have been used previously as a measure of nitric oxide production, despite the potential for nitric oxide-independent effects on cGMP. In addition, there are no data on the effect of anaesthesia on rate-limiting cofactors for NOS and no *in vivo* studies of NOS activity in the CNS during anaesthesia. We therefore investigated the effects of anaesthesia, using a range of agents, on NOS activity and concentrations of tetrahydrobiopterin and cGMP in the rat CNS.

Materials and methods

These investigations were performed in accordance with UK Home Office regulations and all animals remained anaesthetized to a nociceptive stimulus throughout.

Female rats (230–270 g, six per group) were used for all experiments and were maintained on normal rat chow. The

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Table 1 [^{14}C]Citrulline accumulation in regions of the rat central nervous system after i.v. injection of [^{14}C]L-arginine (counts min^{-1} mg^{-1} protein). *Significantly lower than in other regions (P=0.0135)

	Region of central nervous system				
	Spinal cord	**Brainstem**	**Cerebellum**	**Hippocampus**	**Cortex**
Median	142.6*	216.1	273.0	281.8	257.3
Range	120.3–186.8	152.3–376.2	175.8–283.8	158.8–389.9	179.7–382.8

use of a single sex minimizes any differences due to gender, and females do not fight when caged together. Rats were assigned randomly to anaesthesia with halothane 1.5% in oxygen; isoflurane 2% in oxygen; pentobarbital 50 mg kg^{-1} as a bolus followed by 50 mg kg^{-1} h^{-1}; diazepam 10 mg kg^{-1} as a bolus followed by 5 mg kg^{-1} h^{-1}; ketamine 50 mg kg^{-1} as a bolus followed by 50 mg kg^{-1} h^{-1}; or xenon 80% in oxygen. Anaesthesia was induced with either 1.5% halothane (halothane group only) or 2% isoflurane (other groups). After surgical tracheostomy, rats were ventilated to maintain normocapnia ($P\text{CO}_2$ was maintained between 4 and 5 kPa).[7] Saline (5 ml kg^{-1} h^{-1}) was infused continuously via the femoral vein. After surgical preparation, anaesthesia was continued with the allocated agent for 30 min. [^{14}C]L-arginine (Amersham Life Sciences, Amersham, UK) was then administered (15 µCi kg^{-1}=10 mg kg^{-1} L-arginine in saline i.v.). Anaesthesia was continued for a further 60 min. Animals were killed by cervical dislocation and subjected instantaneously to focused microwave radiation to stop all CNS enzyme activity and maintain cGMP levels, as described previously.[8] [9] One group of rats (n=6) were completely untreated (untreated control group) and another group (n=6) received [^{14}C]L-arginine via a tail vein without anaesthesia and were killed 60 min later (treated control group).

The brain was removed and placed in 1 M dithioerythreitol (Sigma, Poole, Dorset, UK) to prevent autooxidation of pterins. The brain was dissected rapidly into the medulla, hippocampus, cerebellum and cerebral cortex. Laminectomy was performed simultaneously and the cervical and thoracic spinal cord were removed. Samples were frozen in liquid nitrogen and stored at -80°C.

Nitric oxide production from an i.v. dose of [^{14}C]arginine (and hence NOS activity during anaesthesia) was measured as labelled citrulline by scintillation counting, as described previously for the measurement of *in vitro* NOS activity.[10] Arginine, including residual labelled arginine, was removed from tissue homogenates before scintillation counting, using a cation exchange column; retention of radiolabelled arginine was consistently >95%.

cGMP was measured using an enzyme immunoassay kit (R&D Systems Europe, Oxford, UK) with prior acetylation of samples and standards to increase assay sensitivity (typically >0.37 pmol ml^{-1}), as recommended by the manufacturer. Intra- and inter-assay precision was 6.2% (n=8) and 6.6% (n=8) respectively.

Tetrahydrobiopterin concentrations were measured by HPLC after selective oxidation with iodine, using a modification of the method described by Fukushima and Nixon.[11] Under acid conditions, all pterins are converted to fluorescent biopterin, whilst under alkali conditions tetrahydrobiopterin is converted to non-fluorescent material, with only biopterin detected. Tetrahydrobiopterin can therefore be measured as the difference between biopterin concentrations under acid and alkali conditions, using HPLC with fluorescent detection.

Prepared samples were injected into a C18 Techsil column (10 µm particle size; HPLC Technology, Macclesfield, Cheshire, UK) using a Gynkotech HPLC system (HPLC Technology). The mobile phase was 10% (v/v) methanol in water and samples were calibrated against biopterin (Sigma), which had also undergone acid–alkali oxidation. Biopterin was detected fluorometrically at excitation and emission wavelengths of 350 and 440 nm respectively. The accuracy of the technique was 78.3 (77.0–79.8)% in recovery experiments (n=30), using 30 ng ml^{-1} biopterin in the presence of 1 mg ml^{-1} bovine serum albumin to mimic tissue protein content. The precision of the assay was 1.8% within runs and 8.1% between runs (n=10).

Results from all assays were expressed in terms of tissue homogenate protein concentration, determined using the Bradford reagent (Sigma).

Statistical analysis

Results are expressed as median and range. Statistical analysis, performed using Microsoft Excel with the Astute statistical add-in, was determined by Kruskal–Wallis analysis of variance with Mann–Whitney *U post hoc* testing as appropriate. P<0.05 was considered significant.

Results

The adequacy of microwave exposure in halting enzyme activity and maintaining cGMP levels was confirmed in preliminary experiments using untreated animals. cGMP concentration, with and without 5 s microwave exposure respectively, was 2.1 (1.7–2.4) and 0.07 (0–0.08) pmol mg^{-1} protein in cerebellum and 2.6 (2.1–3.2) and 0.08 (0–0.08) pmol mg^{-1} protein in spinal cord (n=3).

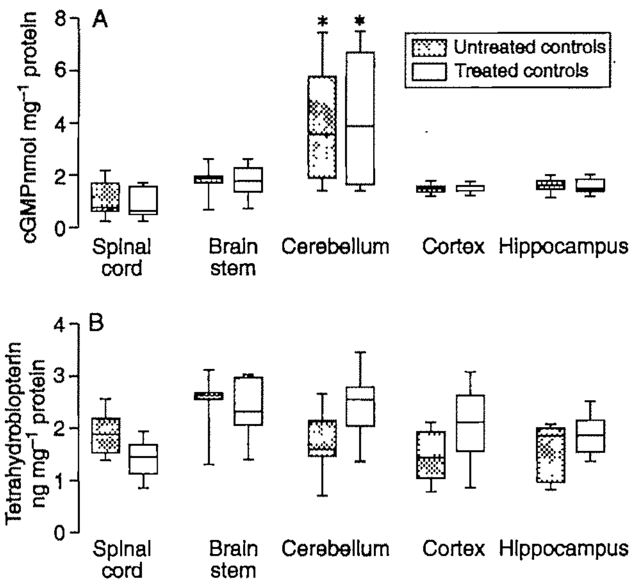

Fig 1 Effect of an i.v. bolus of [^{14}C]L-arginine on cGMP and tetrahydrobiopterin concentrations in regions of the brain and spinal cord in unanaesthetized control rats. Box and whisker plots show median, 25th and 75th centiles and range. Shaded boxes=control animals treated with [^{14}C]L-arginine; empty boxes=untreated controls (n=6 per group). *Significantly different from spinal cord and other brain regions (P<0.05, Mann–Whitney U-test).

Table 1 shows [^{14}C]citrulline accumulation in treated controls (i.e. animals were not anaesthetized but received [^{14}C]arginine). Accumulation in the spinal cord was significantly lower than in other CNS regions (P=0.0135). The effect of i.v. [^{14}C]arginine on cGMP and tetrahydrobiopterin concentrations is shown in Fig. 1. In all brain regions the concentrations of both cGMP (Fig. 1A) and tetrahydrobiopterin (Fig. 1B) after [^{14}C]arginine were unaltered compared with untreated controls (i.e. animals were not anaesthetized and did not receive [^{14}C]arginine). However, the cGMP concentration was higher in the cerebellum than other brain regions or spinal cord (P<0.05) (Fig. 1A).

Effect of anaesthesia

Spinal cord

In the spinal cord, tetrahydrobiopterin concentration was similar in all anaesthetized animals, but was higher than in non-anaesthetized animals (P<0.05) (Fig. 2A). Spinal cord [^{14}C]citrulline accumulation was unaltered by anaesthesia (Fig. 2B). cGMP concentrations in the spinal cord were significantly different after anaesthesia (P<0.0001). *Post hoc* testing revealed that anaesthesia with xenon or ketamine increased cGMP concentration (P<0.05) (Fig. 2C) and halothane and isoflurane anaesthesia decreased cGMP concentration in the spinal cord (P<0.01 and P<0.05 respectively) (Fig. 2C).

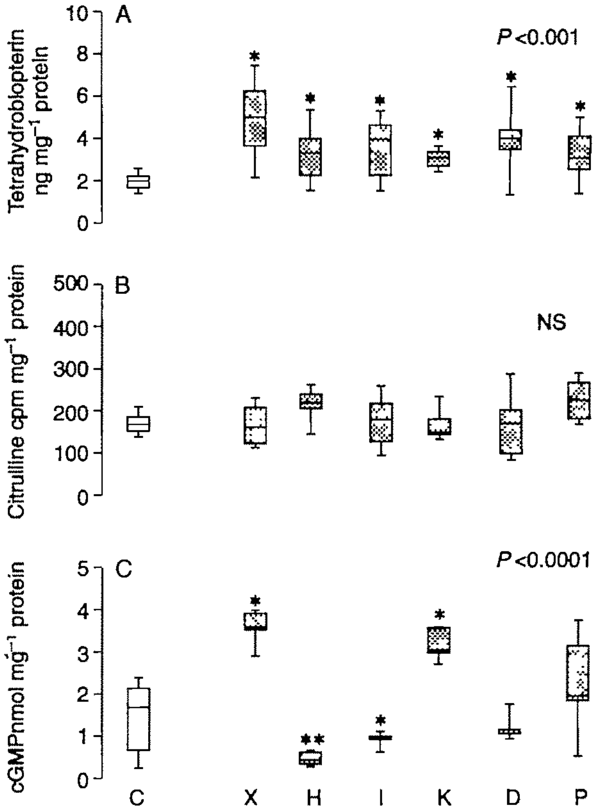

Fig 2 Effect of anaesthesia on (A) tetrahydrobiopterin, (B) [^{14}C]L-citrulline and (C) cGMP concentrations in rat spinal cord after an i.v. dose of [^{14}C]L-arginine. Box and whisker plots show median, 25th and 75th centiles and range. Shaded boxes=anaesthetized animals; empty boxes=unanaesthetized, treated controls (n=6 per group). NS (non-significant) and P values refer to Kruskal–Wallis analysis of variance. C=control; X=xenon; H=halothane; I=isoflurane; K=ketamine; D=diazepam; P=pentobarbital. *Significantly different from unanaesthetized rats (P<0.05, Mann–Whitney U-test); **significantly different from unanaesthetized rats (P<0.01, Mann–Whitney U-test).

Brain

Tetrahydrobiopterin concentrations remained unchanged compared with control rats in the cortex and hippocampus, irrespective of anaesthesia (Fig. 3). However, tetrahydrobiopterin concentrations were altered in the brainstem and cerebellum (P=0.0192 and P=0.0012 respectively) (Fig. 3). On *post hoc* testing, tetrahydrobiopterin was increased after xenon anaesthesia (P<0.05 in brainstem and P<0.01 in cerebellum) (Fig. 3). No other anaesthetics had any effect in these brain regions.

Release of [^{14}C]citrulline (and hence NOS activity during anaesthesia) was not affected by any anaesthetic in any brain region (Fig. 4).

Cyclic GMP concentrations were altered in the brainstem (P=0.0001), cerebellum (P=0.005), cortex (P<0.0001) and hippocampus (P=0.0003) after anaesthesia. As in the spinal cord, xenon or ketamine anaesthesia resulted in significantly increased cGMP concentrations in the brainstem (both P<0.05), cortex and hippocampus (xenon P<0.05, ketamine

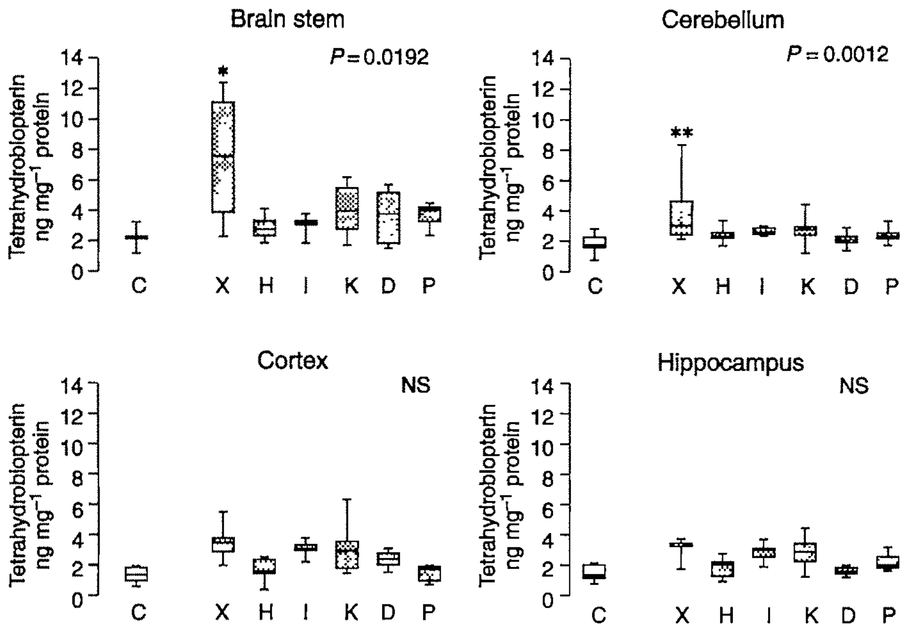

Fig 3 Effect of anaesthesia on tetrahydrobiopterin in rat brain after an i.v. dose of [^{14}C]L-arginine. Box and whisker plots show median, 25th and 75th centiles and range. Shaded boxes=anaesthetized animals; empty boxes=unanaesthetized, treated controls (n=6 per group). NS (non-significant) and P values refer to Kruskal–Wallis analysis of variance. C=control; X=xenon; H=halothane; I=isoflurane; K=ketamine; D=diazepam; P=pentobarbital. *Significantly different from unanaesthetized rats (P<0.05, Mann–Whitney U-test); **significantly different from unanaesthetized rats (P<0.01, Mann–Whitney U-test).

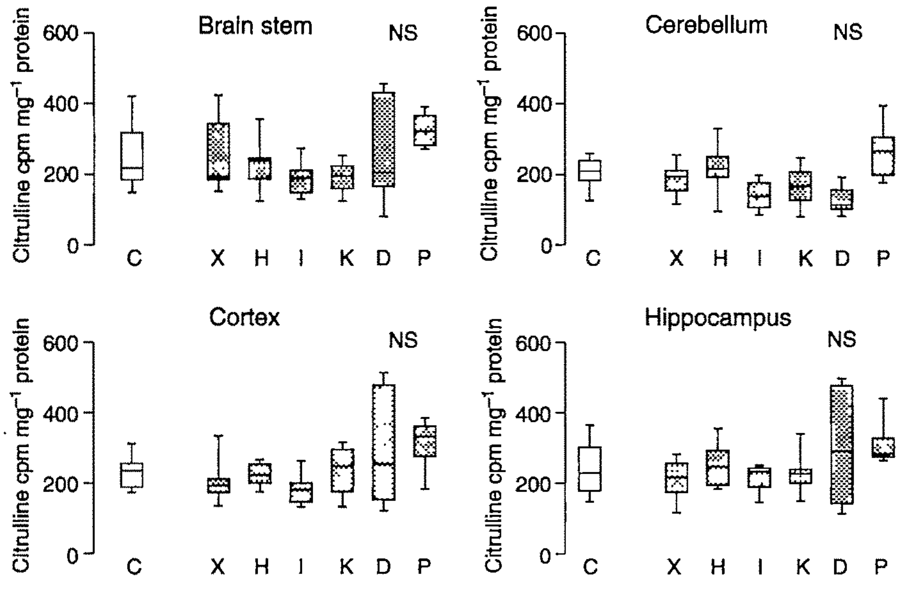

Fig 4 Effect of anaesthesia on [^{14}C]L-citrulline in the rat brain after an i.v. dose of [^{14}C]L-arginine. Box and whisker plots show median, 25th and 75th centiles and range. Shaded boxes=anaesthetized animals; empty boxes=unanaesthetized, treated controls (n=6 per group). NS (non-significant) refers to Kruskal–Wallis analysis of variance. C=control; X=xenon; H=halothane; I=isoflurane; K=ketamine; D=diazepam; P=pentobarbital.

P<0.01). Halothane anaesthesia resulted in decreased cGMP concentrations in all brain regions (P<0.05 in brainstem and cerebellum, P<0.01 in cortex and hippocampus). Isoflurane decreased cGMP concentrations in the cerebellum and cortex (both P<0.05) (Fig. 5).

Discussion

We found that halothane and isoflurane decreased cGMP concentrations in the spinal cord and most brain regions. In contrast, ketamine and xenon anaesthesia increased cGMP

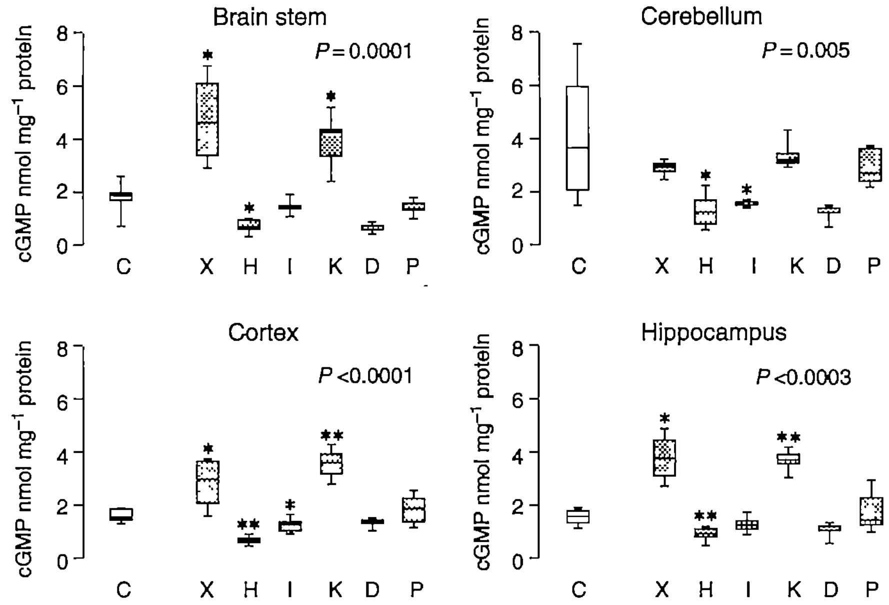

Fig 5 Effect of anaesthesia on cGMP in rat brain after an i.v. dose of [^{14}C]L-arginine. Box and whisker plots show median, 25th and 75th centiles and range. Shaded boxes=anaesthetized animals; empty boxes=unanaesthetized, treated controls (n=6 per group). P values refer to Kruskal–Wallis analysis of variance. C=control; X=xenon; H=halothane; I=isoflurane; K=ketamine; D=diazepam; P=pentobarbital. *Significantly different from unanaesthetized rats (P<0.05, Mann–Whitney U-test); **significantly different from unanaesthetized rats (P<0.01, Mann–Whitney U-test).

concentrations in the brain and spinal cord. However, NOS activity, measured as [^{14}C]L-citrulline after an i.v. dose of [^{14}C]L-arginine, was unaffected by any of the anaesthetic agents tested. Tetrahydrobiopterin concentration was increased in anaesthetized animals, independently of the anaesthetic used.

A technique similar to that described here was used by Northington *et al.* to measure *in vivo* nitric oxide release in the brain, although labelled arginine was directly infused into sheep cerebellum using a microdialysis probe.[12] These authors found increased nitric oxide release in response to *N*-methyl-D-aspartate (NMDA) and decreased nitric oxide after an NOS inhibitor was adminstered.[12] In the present study, we administered [^{14}C]arginine i.v. as a bolus dose to quantify nitric oxide release, and hence NOS activity, across a defined time window. We have demonstrated the accumulation of [^{14}C]citrulline in the brain and spinal cord after an i.v. dose of labelled L-arginine, indicating that [^{14}C]L-arginine was able to reach the CNS. Administration of labelled arginine had no effect on concentrations of either cGMP or tetrahydrobiopterin, as no difference was seen between treated and untreated control rats, and all subsequent comparisons were made using unanaesthetized animals that had received [^{14}C]arginine. Labelled citrulline concentration was lowest in the spinal cord, which may reflect either differences in the delivery of i.v. arginine to the spinal cord compared with the brain, or genuinely lower nitric oxide production in the spinal cord than in the brain. A previous study using the *in vitro* conversion of [^{14}C]arginine to [^{14}C]citrulline also reported lower NOS activity in the spinal cord than in the brain,[13] as in the present study.

The anaesthetic agents used in the present study were chosen for their differing chemical structures and disparate suggested modes of action. Xenon is an inert gas that inhibits NMDA receptor channels.[14] Halothane is a halogenated hydrocarbon that is approximately 25–30% metabolized. Isoflurane is a fluorinated ether and is less than 5% metabolized. Ketamine is an NMDA receptor antagonist, diazepam acts at the benzodiazepine site on GABA$_A$ receptors, and pentobarbital is a short-acting barbiturate that is thought to act at GABA$_A$ receptors. We found that citrulline from [^{14}C]arginine, and hence NOS activity during the time window of the study, was not affected by any of the anaesthetics studied. Previous *in vitro* studies have produced conflicting results. A direct inhibitory effect of halothane and isoflurane on NOS activity in the rat brain[5] and of halothane on human leucocytes[15] has been described *in vitro*. However, other studies found no effect of halothane, isoflurane or enflurane on rat brain NOS.[16] Ketamine and pentobarbital had no effect on rat brain NOS activity in one study[5] but inhibited activity in another study.[4] Different techniques, which included citrulline accumulation and the conversion of oxy- to met-haemoglobin, were used in these *in vitro* studies. Both are accepted, validated techniques for the indirect quantification of NOS activity. The present study used the conversion of exogenous [^{14}C]L-arginine to [^{14}C]L-citrulline in a physiological *in vivo* situation, as used in a previous study in sheep.[12] An improved version of the *in vitro* citrulline assay also confirmed no direct effect of halothane on the activity or kinetics of NOS isolated from the rat CNS.[13] Of course, nitric oxide production from brain homogenates in an artificial *in vitro* situation may not reflect effects *in vivo*.

In our *in vivo* study we found that both halothane and isoflurane anaesthesia markedly decreased cGMP concentrations throughout the rat CNS. There have been conflicting results from previous studies of the effects of anaesthetics on cGMP, and the majority of these studies have been *in vitro*.[17 18] It has been shown that hypercapnia and hypoxia have profound effects on nitric oxide and cGMP,[19 20] which illustrates the need to maintain normal arterial blood gas values. In the present study normocapnia was maintained, so the changes we observed in cGMP were not the result of ventilation-induced hypercapnia. Potential non-specific post-mortem changes in cGMP were eliminated using microwave irradiation, as described previously.[8 9]

The decreased cGMP concentration reported previously in anaesthetized, treated animals has been attributed to altered motor function as a result of anaesthesia/sedation, as paralysis for 15 min also decreased cGMP,[21] and increased locomotor activity induced by tremors and seizures[9] or forced running[22] increased cGMP. However, we found that cGMP concentration was decreased by halothane and isoflurane, was unaltered by pentobarbital and diazepam, and was increased by ketamine and xenon. Interestingly, in the present study, we noted that, although nociceptive responses were abolished during xenon and ketamine anaesthesia, some degree of spontaneous motor function was retained.

In rat cerebellar slices *in vitro*, ketamine was found to depress NMDA or glutamate-stimulated cGMP but not non-receptor-mediated cGMP accumulation.[23] We found increased cGMP concentrations in response to the NMDA receptor antagonists ketamine and xenon. It might be expected that these agents would cause decreased cGMP accumulation by blocking NMDA-receptor mediated NOS activation. However, a recent study using microdialysis probes in the brains of intact rats reported that products of nitric oxide are increased during administration of ketamine, but cGMP was not measured.[6] There are no previous studies of the effects of xenon on cGMP.

Alterations in cGMP can occur through mechanisms other than altered nitric oxide release. Soluble guanylate cyclase, the enzyme that catalyses the conversion of GTP to cGMP, is activated about 400-fold by nitric oxide, about 20-fold by hydroxyl ions and about 4-fold by carbon monoxide. However, it is the regulation of cGMP concentration via phosphodiesterases, which catalyse the breakdown of cGMP to 5′-GMP, that is likely to be particularly important. In the present study, microwave radiation will not only inactivate guanylate cyclase, thus terminating further cGMP production, but will also inactivate phosphodiesterases and hence terminate further cGMP breakdown. The effect of anaesthetic agents on phosphodiesterases remains unknown. The altered cell membrane function that has been reported in response to some anaesthetics[24] could also lead to the intracellular accumulation of cGMP. In the present study, this will manifest as an increase in cGMP in brain homogenates, but in *in vitro* studies the effect would appear as decreased release of cGMP into the incubation medium.

We found that tetrahydrobiopterin concentrations increased in the spinal cord in all anaesthetized rats and in some brain areas after anaesthesia with xenon. These changes were not associated with NOS activity measured as [^{14}C]citrulline accumulation, suggesting that NOS does not occur in the same distribution as sites of tetrahydrobiopterin synthesis. The significance of these findings is unclear. Tetrahydrobiopterin is also a cofactor for tyrosine and tryptophan hydrolases, and *in situ* hybridization has shown that GTP-cyclohydrolase, the rate-limiting enzyme for tetrahydrobiopterin synthesis, is co-localized with these enzymes and not with NOS, suggesting that nitric oxide-producing cells may obtain their tetrahydrobiopterin from that released into the circulation.[25] There are no previous data on the effects of anaesthetics, either *in vivo* or *in vitro*, on biopterins. However, it has been shown that prolonged hypoxia increases cerebellar nitric oxide formation, through up-regulation of GTP cyclohydrolase I expression and hence tetrahydrobiopterin levels,[26] again emphasizing the importance of maintaining $P\text{O}_2$ and $P\text{CO}_2$ within normal limits. Alteration of cell membrane function or transport systems for secreted products by anaesthetics[24 27] may also lead to the accumulation of cell products such that concentrations appear increased.

In summary, we have shown that anaesthesia affects cGMP production in the rat brain and spinal cord. The discrepancy between the changes in cGMP in the absence of altered NOS activity, measured as [^{14}C]citrulline production or tetrahydrobiopterin concentrations, suggests that these effects may act via nitric oxide-independent cGMP regulation, possibly through effects on the metabolism of cGMP.

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Suppressive effect of nitrous oxide on motor evoked potentials can be reversed by train stimulation in rabbits under ketamine/ fentanyl anaesthesia, but not with additional propofol

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The effect of nitrous oxide on myogenic motor evoked potentials (MEPs) after multipulse stimulation is controversial. We investigated the effects of propofol in this paradigm. MEPs were elicited electrically by a single pulse and by trains of three and five pulses in rabbits anaesthetized with ketamine and fentanyl. Nitrous oxide 30–70% was given and MEPs were recorded. After washout of nitrous oxide, propofol was given as a bolus of 10 mg kg^{-1} followed by 0.8 (n=9) or 1.6 mg kg^{-1} min^{-1} (n=8) as a continuous infusion. Nitrous oxide was then re-administered and MEPs were recorded. Without propofol, nitrous oxide significantly reduced the amplitude of MEPs dose-dependently, but this effect was reversed by multipulse stimulation. Administration of low-dose propofol enhanced nitrous oxide-induced suppression, and this effect was reversed by five-pulse stimulation. However, high-dose propofol produced a greater increase in suppression, such that even five-pulse stimulation did not overcome the suppression. The results suggest that the degree of reversal of nitrous oxide-induced MEP suppression produced by multipulse stimulation is affected by the administration of propofol.

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Intraoperative monitoring of myogenic motor evoked potentials (MEPs) in response to transcranial stimulation of the motor cortex provides a method for monitoring the functional integrity of descending motor pathways during invasive manipulation of the spine or thoracoabdominal aortic replacement surgery.[1–3] However, the clinical and experimental use of these techniques with a single pulse as the stimulus has shown that the potentials elicited are very sensitive to suppression by most anaesthetic agents.[4–7] Recently, to overcome anaesthetic-induced depression of myogenic MEPs, multiple-stimulus setups with paired or a train of pulses for stimulation of the motor cortex have been proposed.[8–13] The advent of multipulse stimulation for intraoperative monitoring of myogenic MEPs may allow a wider choice and dose range of anaesthetic agents.

Nitrous oxide has been used commonly during MEP monitoring as a supplementary anaesthetic,[2 3 6 8 12–14] although a number of investigators have shown that it suppresses MEPs elicited by single-pulse stimulation.[15–18] However, the effect of nitrous oxide on myogenic MEPs in response to stimulation with paired pulses or a train of pulses is still controversial.[19–21] One report demonstrated that 50% nitrous oxide did not affect the amplitude of MEPs under fentanyl/low-dose propofol anaesthesia when paired-pulse stimulation was applied.[19] By contrast, other reports have shown that, even with a train of six pulses, increasing the concentration of nitrous oxide to 60% resulted in reduced MEP amplitude.[21] These controversial results suggest that the reversing effect of multipulse stimulation on nitrous oxide-induced suppression of MEPs may be overcome by adding more anaesthetic in the form of propofol. However, there has been no report confirming this hypothesis, probably because many permutations of nitrous oxide concentration, propofol infusion rate and stimulus train size would make this difficult to study in surgical patients.

The present study was conducted to investigate the effects of nitrous oxide on myogenic MEPs when multipulse stimulation was applied in rabbits under ketamine/fentanyl anaesthesia, which produces minimal depression of MEP.[4 14 21] Furthermore, we infused propofol at two rates (low- and high-dose regimens) with nitrous oxide to elucidate the above controversy about the reversing effect of multipulse stimulation on nitrous oxide-induced MEP suppression.

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Table 1 Physiological variables. Data are mean (SEM). *$P<0.01$ *vs* before propofol

	Nitrous oxide (%)				
	0	**30**	**50**	**70**	**Re-zeroed**
Mean arterial pressure (mm Hg)					
Propofol 0.8 (*n*=9)					
Before	84 (4)	83 (4)	87 (4)	90 (4)	83 (4)
During	86 (4)	87 (5)	89 (3)	90 (3)	82 (3)
Propofol 1.6 (*n*=8)					
Before	80 (4)	80 (5)	82 (5)	88 (5)	83 (3)
During	90 (5)	87 (3)	89 (4)	88 (3)	92 (2)
Heart rate (beats min^{-1})					
Propofol 0.8 (*n*=9)					
Before	250 (11)	250 (7)	273 (9)	272 (12)	255 (9)
During	234 (7)	250 (11)	254 (12)	254 (15)	251 (9)
Propofol 1.6 (*n*=8)					
Before	249 (12)	237 (11)	257 (12)	258 (15)	247 (10)
During	215 (8)*	208 (19)*	231 (11)*	246 (12)	221 (4)*
Oesophageal temperature (°C)					
Propofol 0.8 (*n*=9)					
Before	40.3 (0.2)	40.4 (0.2)	40.3 (0.1)	40.3 (0.2)	40.3 (0.2)
During	40.3 (0.2)	40.1 (0.2)	40.1 (0.2)	40.1 (0.2)	40.1 (0.2)
Propofol 1.6 (*n*=8)					
Before	39.9 (0.1)	39.9 (0.1)	39.8 (0.1)	39.7 (0.1)	39.8 (0.2)
During	39.8 (0.2)	39.7 (0.2)	39.7 (0.3)	39.8 (0.2)	39.8 (0.2)

Materials and methods

The study was approved by the Animal Experiment Committee of Nara Medical University. Seventeen male New Zealand White rabbits weighing 2.0–2.5 kg (mean 2.3 kg) were used. They were housed and maintained on a 12 h light–dark cycle with free access to food and water.

Each rabbit was given ketamine 50 mg kg^{-1} i.m. and a 24-gauge catheter was placed in the right marginal ear vein. Thereafter, continuous infusion of ketamine 25 mg kg^{-1} h^{-1} and fentanyl 30 µg kg^{-1} h^{-1} in lactated Ringer solution was initiated at the rate of 4 ml kg^{-1} h^{-1}. Another 24-gauge catheter was inserted in the left ear vein for the administration of propofol. The trachea was intubated via a tracheostomy and the lungs were ventilated mechanically to maintain end-tidal carbon dioxide at 30–35 mm Hg. End-tidal concentrations of carbon dioxide and nitrous oxide were monitored continuously with a gas analyser (Hewlett Packard, Andover, MA, USA). The left femoral artery was exposed and cannulated to monitor arterial blood pressure and for blood gas analysis. Blood gases, pH and haematocrit were measured periodically with a blood gas analyser (GEM Premier; Mallinckrodt, Ann Arbor, MI, USA). Oesophageal temperature was monitored continuously with a thermometer (Mon-a-Therm, Mallinckrodt, St Louis, MO, USA) and maintained at 40°C with a warm blanket.

The animals were placed prone and the head was fixed in a stereotactic frame. The scalp was infiltrated with 1% lidocaine and reflected laterally to expose the calvarium. Two small craniotomies were performed with an air drill. A point 0.5 mm lateral to the sagittal suture and 14.5 mm rostral to the lamboid suture on the left hemisphere was chosen as the anodal stimulating site.[22] A point 0.5 mm to the right of the sagittal suture at the level of the lamboid suture was used for the cathode. Silver ball electrodes (1 mm in diameter) were placed epidurally via holes, in which mineral oil was placed. Two standard recording needle electrodes were inserted in the left soleus muscle. A ground electrode was placed at the tail. Constant-voltage anodal stimulation was delivered through an electrical stimulator (SEN-3301; Nihon Kohden, Tokyo, Japan). The strength of the electrical stimulus was increased gradually until MEP amplitude no longer increased. The recording device (Neuropack Sigma, Nihon Kohden) was triggered by the stimulating device. Low- and high-cutoff filters were set at 30 Hz and 3 kHz respectively. Peak-to-peak amplitude was determined from the average of three to five individual responses. After the MEPs in response to a single-pulse stimulation had been recorded, a train of three or five pulses was applied. The duration of each pulse was 200 µs. The interstimulus interval of each pulse was set at 2 ms. The interval between each stimulation was set at 30 s.

After control MEPs had been recorded, nitrous oxide was administered at a concentration of 30, 50 or 70%. The order of concentrations was randomized to eliminate time-course bias. At least 10 min was allowed to elapse between each targeted concentration, and the end-tidal concentration of nitrous oxide was confirmed with a gas analyser. At each concentration of nitrous oxide, MEPs in response to a single pulse and a train of three or five pulses were recorded. After completion of all recordings at the three concentrations of nitrous oxide, administration of nitrous oxide was discontinued. MEPs were again recorded when the end-tidal

Table 2 Blood gas analysis before and during administration of propofol. Data are mean (SEM)

	pH	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	Haematocrit (%)
Propofol 0.8 (*n*=9)				
Before	7.43 (0.03)	35 (1)	440 (44)	32 (2)
During	7.31 (0.02)	36 (1)	466 (42)	32 (1)
Propofol 1.6 (*n*=8)				
Before	7.36 (0.02)	35 (2)	413 (19)	32 (2)
During	7.33 (0.03)	37 (2)	484 (32)	29 (2)

concentration of nitrous oxide was 0%, as assessed by the gas analyser.

After the complete elimination of nitrous oxide, all animals were allocated randomly to one of two groups. In one group (Propofol 0.8, *n*=9), a bolus of propofol 10 mg kg^{-1} was administered, followed by a continuous infusion of propofol at 0.8 mg kg^{-1} min^{-1}. In the other group (Propofol 1.6, *n*=8), a bolus of propofol 10 mg kg^{-1} was followed by a continuous infusion of propofol at 1.6 mg kg^{-1} min^{-1}. Thirty minutes after administration of the bolus of propofol, nitrous oxide was administered at 30, 50 or 70% and MEPs were recorded in the same fashion as described above. During administration of propofol, a continuous infusion of phenylephrine was given if arterial blood pressure decreased by more than 10% of control. At the end of the study, the animals were killed with an injection of potassium chloride, which caused cardiac arrest.

Statistical analysis

All values are expressed as mean (SEM). Parametric methods were used for the analysis of all variables, as a normal distribution was confirmed with the Kolmogorov–Smirnov test. For comparisons of physiological variables and MEP amplitudes between the two experimental groups, we used two-way analysis of variance with repeated measures followed by Fisher's protected least significant difference test for multiple comparisons. To compare values within groups, we used multiple analysis of variance with repeated measures followed by Fisher's protected least significant difference test for multiple comparisons. Differences were considered significant when $P<0.05$.

Results

Physiological variables are shown in Tables 1 and 2. There were no significant differences between the two experimental groups in mean arterial pressure (MAP), heart rate, oesophageal temperature, pH, Pa_{CO_2} and Pa_{O_2} before the administration of propofol. With the exception of heart rate, all variables were similar in the two groups during the administration of propofol. Heart rate was significantly reduced during the administration of propofol 1.6 mg kg^{-1} min^{-1} ($P<0.01$). MAP, heart rate and oesophageal temperature did not change significantly before, during or after the administration of nitrous oxide. Phenylephrine was used in all animals in both groups during propofol infusion; the doses were approximately 0.05–0.7 (mean 0.33) mg h^{-1} for the Propofol 0.8 group and 0.1–1.5 (mean 0.6) mg h^{-1} for the Propofol 1.6 group.

The effect of propofol on MEPs

Distinct MEPs could be recorded in all animals before the administration of propofol, and there were no significant differences between the two groups in the amplitudes of MEPs in response to stimulation with a single pulse or a train of three or five pulses. The changes in the amplitudes of MEPs induced by electrical stimulation with a single pulse or a train of three or five pulses in the two groups are shown in Fig. 1.

During the administration of propofol 0.8 mg kg^{-1} min^{-1}, MEPs could be recorded in all animals, and the amplitude of MEPs in response to single-pulse stimulation was significantly reduced ($P<0.05$). MEP amplitudes in response to stimulation with a train of three or five pulses were not significantly different from baseline during administration of propofol 0.8 mg kg^{-1} min^{-1}.

During the administration of propofol 1.6 mg kg^{-1} min^{-1}, MEPs could be recorded in only three of eight animals after single-pulse stimulation. By contrast, MEPs could be recorded in all animals after stimulation with a train of three or five pulses, and MEP amplitudes were significantly higher than after single-pulse stimulation ($P<0.01$). The amplitudes of MEPs after stimulation with a single pulse or a train of three or five pulses were significantly reduced during propofol administration ($P<0.01$).

For later analysis of the effects of nitrous oxide and number of pulses, data on MEPs before the administration of propofol in both groups were pooled as group Propofol(–).

Effects of nitrous oxide on MEPs

Propofol(–)

Without administration of propofol, the amplitudes of MEPs in response to stimulation with a single pulse or a train of three pulses were significantly reduced after the administration of 50% ($P<0.01$) or 70% ($P<0.01$) nitrous oxide and after 70% ($P<0.05$) nitrous oxide, respectively (Fig. 2). By

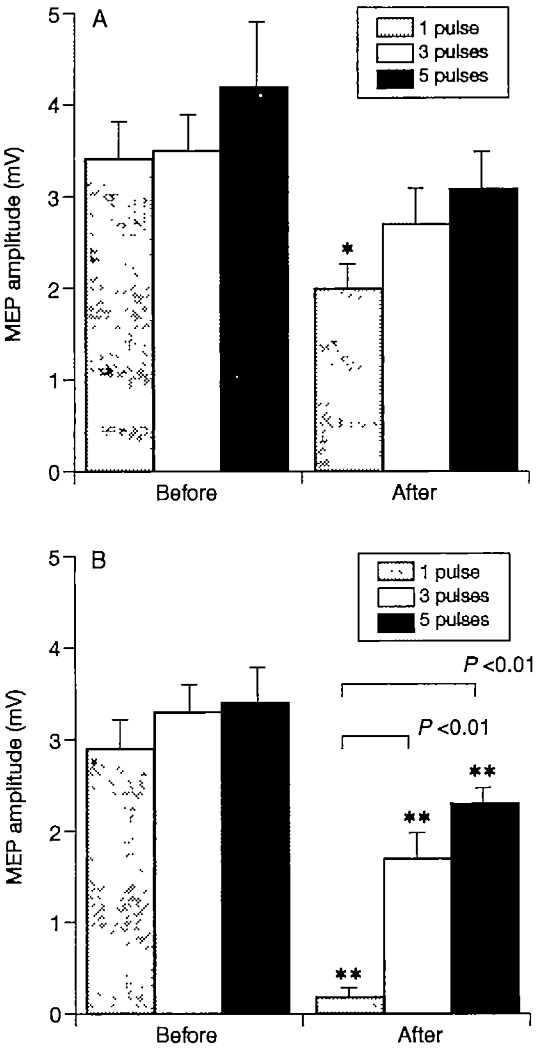

Fig 1 Changes in amplitude of myogenic MEPs in response to electrical stimulation with a single pulse or a train of three or five pulses before and during the administration of propofol in rabbits under ketamine/fentanyl anaesthesia. Propofol was administered as a bolus of 10 mg kg^{-1} followed by continuous infusion at 0.8 mg kg^{-1} min^{-1} (A) or 1.6 mg kg^{-1} min^{-1} (B). Data are expressed as mean (SEM). *$P<0.05$ *vs* before propofol; **$P<0.01$ *vs* before propofol.

contrast, the amplitudes of MEPs induced by a stimulation with a train of five pulses did not change significantly during the administration of nitrous oxide (Fig. 3). The amplitudes of MEPs in response to a stimulation with a train of three pulses during 70% nitrous oxide and a train of five pulses during administration of 30, 50 or 70% nitrous oxide were significantly higher than those after single-pulse stimulation.

Propofol 0.8

During the administration of propofol 0.8 mg kg^{-1} min^{-1}, MEPs in response to single-pulse stimulation could be recorded in six, four and one of nine animals during the administration of 30, 50 and 70% nitrous oxide respectively. During the administration of nitrous oxide, the amplitudes

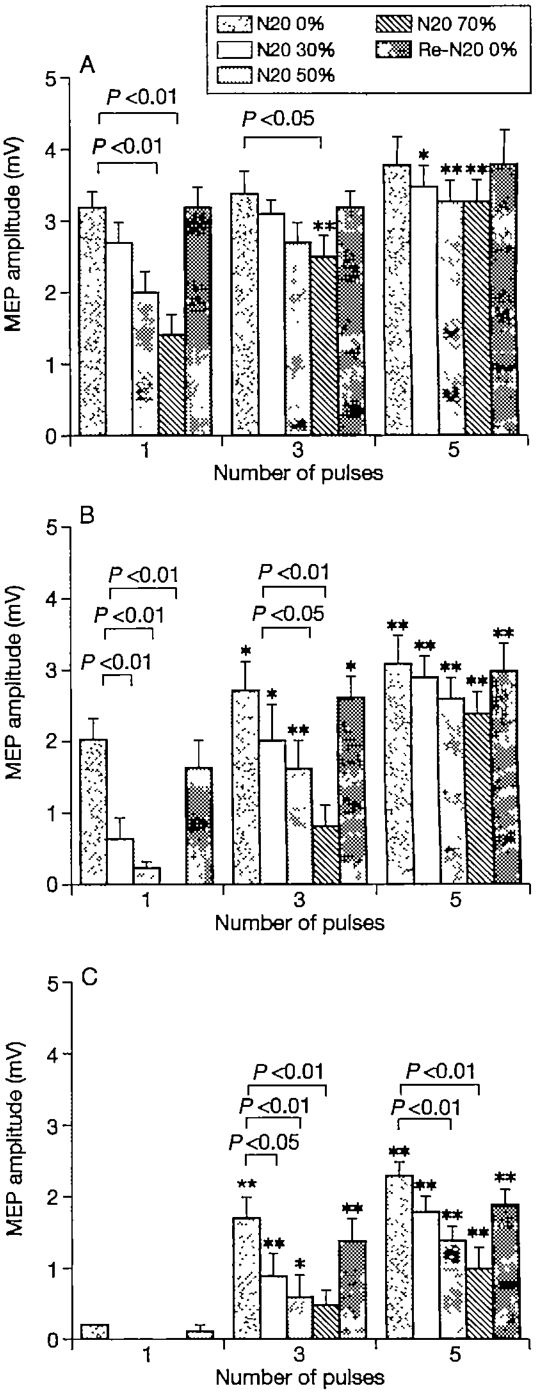

Fig 2 Effects of nitrous oxide on amplitude of myogenic MEPs without (A) and with (B, C) propofol administration in rabbits under ketamine/fentanyl anaesthesia. Electrical stimulation was performed with a single pulse or a train of three or five pulses. After a control recording, the concentration of nitrous oxide (N_2O) was changed to 30, 50 or 70% and then re-zeroed. Propofol was administered as a bolus of 10 mg kg^{-1} followed by continuous infusion at 0.8 mg kg^{-1} min^{-1} (B) or 1.6 mg kg^{-1} min^{-1} (C). Data are expressed as mean (SEM). *$P<0.05$ *vs* one pulse; **$P<0.01$ *vs* one pulse.

of MEPs in response to single-pulse stimulation were significantly reduced in a dose-dependent manner ($P<0.01$) (Fig. 2). However, amplitudes returned to the baseline after

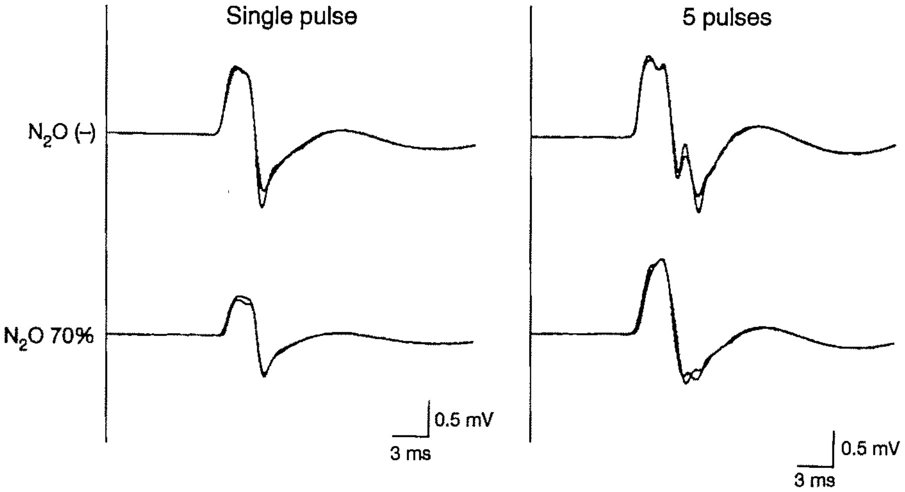

Fig 3 Representative MEPs induced by stimulation with a single pulse or a train of five pulses before the administration of nitrous oxide [N_2O(–)] and after 70% nitrous oxide (N_2O 70%) in a rabbit under ketamine/fentanyl anaesthesia. Administration of 70% nitrous oxide significantly reduced the amplitude of MEPs in response to single-pulse stimulation. By contrast, the amplitude of MEPs in response to stimulation with a train of five pulses did not change significantly.

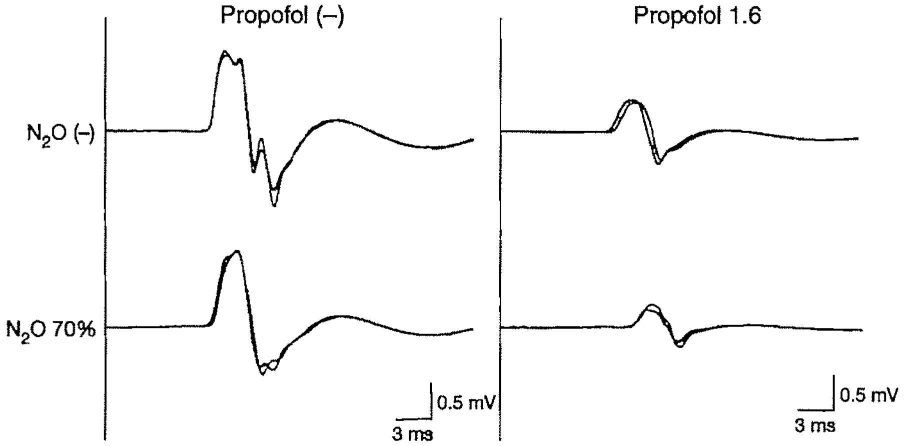

Fig 4 Representative MEPs induced by stimulation with a train of five pulses before [Propofol(–), N_2O(–)] and after (Propofol 1.6, N_2O 70%) the administration of propofol and/or nitrous oxide in a rabbit under ketamine/fentanyl anaesthesia. Propofol was administered as a bolus (10 mg kg^{-1}) followed by continuous infusion (1.6 mg kg^{-1} min^{-1}). Before the administration of propofol, the amplitude of MEPs did not change significantly during administration of 70% nitrous oxide. By contrast, administration of 70% nitrous oxide significantly reduced the amplitude of MEPs during propofol administration.

nitrous oxide was discontinued. MEPs in response to stimulation with a train of three or five pulses could be recorded in all animals during the administration of nitrous oxide, but not in two animals after stimulation with a train of three pulses during administration of 70% nitrous oxide. The amplitudes of MEPs after stimulation with a train of three pulses were significantly reduced during the administration of 50% ($P<0.05$) or 70% ($P<0.01$) nitrous oxide. The amplitudes of MEPs in response to stimulation with a train of five pulses did not change significantly during propofol administration. The amplitudes of MEPs in response to stimulation with a train of three pulses during 30 or 50% nitrous oxide or a train of five pulses during 30, 50 or 70% nitrous oxide were significantly higher than those after single-pulse stimulation.

Propofol 1.6

During the administration of propofol 1.6 mg kg^{-1} min^{-1}, MEPs in response to a single pulse could be recorded only in the absence of nitrous oxide. MEPs in response to stimulation with a train of three pulses could be recorded in eight, five and four of eight animals during the administration of 30, 50 and 70% nitrous oxide respectively. MEPs could be recorded in all animals in response to stimulation with a train of five pulses. During the administration of nitrous oxide, the amplitudes of MEPs in response to stimulation with a train of three or five pulses were significantly reduced in a dose-dependent manner (Figs 2 and 4). The amplitudes of MEPs in response to stimulation with a train of three pulses during 30 or 50% nitrous oxide or with a train of five pulses during the administration of nitrous oxide were significantly higher than those after single-pulse stimulation.

Discussion

Results obtained in the present study show that nitrous oxide dose-dependently reduced the amplitudes of MEPs in response to single-pulse stimulation in rabbits anaesthetized with ketamine and fentanyl, and that this effect was reversed by the application of a train of pulses. After the administration of propofol 0.8 mg kg^{-1} min^{-1}, significant nitrous oxide-induced suppression was observed in the amplitudes of MEPs in response to stimulation with a single pulse or a train of three pulses, but not with a train of five pulses. However, after the administration of propofol 1.6 mg kg^{-1} min^{-1}, significant nitrous oxide-induced suppression was noted even after a train of five pulses. These results suggest that the reversing effect of multipulse stimulation on nitrous oxide-induced suppression of MEPs was overcome by high-dose administration of propofol.

In previous work that investigated the effects of nitrous oxide on myogenic MEPs,[15–18] the dose-dependence of the suppressive effect of nitrous oxide on MEPs in response to single-pulse stimulation has often been demonstrated,[15–18] regardless of differences in combined anaesthetic regimens. These reports are compatible with the present results, which were obtained with ketamine/fentanyl anaesthesia. However, there have been few reports on the effect of nitrous oxide on myogenic MEPs when paired pulses or a train of pulses were used for stimulation, and the results are controversial.[19–21] Van Dongen *et al.*[19] compared MEPs in response to a six-pulse train of transcranial electrical stimuli when 20, 40 or 60% nitrous oxide was given in 10 patients anaesthetized with fentanyl and low-dose propofol. Compared with 20% nitrous oxide, 40 or 60% nitrous oxide significantly reduced MEP amplitude. Pechstein *et al.*[20] also reported that 60% nitrous oxide significantly reduced the amplitude of MEPs induced by transcranial stimulation with a train of five pulses in four patients anaesthetized with alfentanil and propofol. By contrast, in another report by van Dongen *et al.*,[21] it was noted that 50% nitrous oxide did not affect the amplitude of MEPs induced by transcranial electrical stimulation with paired pulses during fentanyl and low-dose propofol anaesthesia in 10 patients. The reasons for the different results are unknown. However, it is possible that co-administration of propofol with nitrous oxide affected the results.

In the present study, the degree of reversal of the effect of nitrous oxide-induced suppression of multipulse stimulation was affected by propofol. In the absence of propofol, nitrous oxide-induced suppression could be reversed after the application of a train of five pulses. A similar tendency was also observed during the administration of propofol at 0.8 mg kg^{-1} min^{-1} (low dose). However, when the propofol infusion rate was increased to 1.6 mg kg^{-1} min^{-1} (high dose), even a train of five pulses was unable to reverse the nitrous oxide-induced suppression of MEPs. These findings may be important for the determination of the optimal combination of anaesthetics during intraoperative MEP monitoring. Our data in a rabbit model suggest that, when nitrous oxide is used as a supplement, high-dose propofol is probably better avoided. In contrast, when multipulse stimulation is used the effect of nitrous oxide on MEPs may be minimal during low-dose administration of propofol in the rabbit MEP model.

For ethical reasons, a baseline anaesthetic was necessary. We selected ketamine and fentanyl because both drugs have minimal effects on MEPs,[4 13 14 23 24] although Thees *et al.*[25] have recently reported a dose-dependent suppressive effect of fentanyl. However, the dosage of fentanyl used in the present experiment was much lower than that used in their study. Moreover, there was evidence that, with this regimen, multipulse stimulus resulted in maximal MEP amplitudes, suggesting near-maximal recruitment of cortical and spinal motor neurones.

Our propofol regimen comprised a bolus of 10 mg kg^{-1} followed by continuous infusion at 0.8 or 1.6 mg kg^{-1} min^{-1}. These doses were selected on the basis of the results of a preliminary study that we made (unpublished), in which the basic procedure was identical to that used in the present study. Infusion rates after a bolus of propofol 10 mg kg^{-1} were doubled from 0.1 to 3.2 mg kg^{-1} min^{-1} in a step-wise manner. Amplitudes of MEPs in response to single-pulse stimulation were recorded 30 min after each step. On the basis of the results obtained, in the present study we chose 0.8 mg kg^{-1} min^{-1} as the low-dose regimen, which resulted in a mild reduction in MEP amplitude, and 1.6 mg kg^{-1} min^{-1} as the high-dose regimen, which produced a severe reduction in MEP amplitude. These doses were similar to those used in a previous study in which a mean propofol infusion rate of 0.876 mg kg^{-1} min^{-1} produced a light plane of anaesthesia in which the palpebral reflex, the reaction to ear pinching, and the front and hind limb withdrawal reflexes were abolished in rabbits.[26]

Ma *et al.*[27] measured the blood concentration of propofol when propofol was infused at 0.8 mg kg^{-1} min^{-1} in rabbits. They demonstrated that the blood concentration remained constant from 15 min after starting the infusion until the withdrawal of propofol at 105 min. In our study, MEP recording began 30 min after the propofol infusion and was completed within 120 min. Therefore, we believe that blood concentration was constant during the administration of propofol 0.8 mg kg^{-1} min^{-1}. By contrast, regarding propofol 1.6 mg kg^{-1} min^{-1}, we cannot exclude the possibility that the variation in blood propofol concentration observed during the administration of propofol 1.6 mg kg^{-1} min^{-1} affected the results obtained in the present study. In order to avoid time-course bias, the order of administration of the different nitrous oxide concentrations was randomized. Moreover, we measured MEP amplitudes again after nitrous oxide had been discontinued, and did not find any differences between the values obtained before and after the administration of nitrous oxide. Therefore, we believe that the influence of variation in propofol concentration on MEPs was minimal.

In summary, we have investigated the influence of stimulation paradigm and the administration of propofol on the nitrous oxide-induced suppression of myogenic MEPs in rabbits anaesthetized with ketamine and fentanyl. We have demonstrated that the application of a train of five pulses reverses nitrous oxide-induced suppression of MEPs in the absence of propofol infusion and during the administration of low- but not high-dose propofol. These results suggest that nitrous oxide-induced suppression of MEPs can be modified by the use of multipulse stimulation and the administration of propofol. Further clinical investigations are required to determine optimal anaesthetic regimens for intraoperative MEP monitoring.

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Evaluation and comparison of the pharmacokinetic and pharmacodynamic properties of allopregnanolone and pregnanolone at induction of anaesthesia in the male rat

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We have evaluated and compared the pharmacokinetic and pharmacodynamic properties of allopregnanolone and pregnanolone at induction of anaesthesia in male rats. A threshold method was used, and the first burst suppression period of 1 s or more in the EEG was selected as the end-point after fairly slow infusions. An optimal dose of 4.0 mg kg^{-1} min^{-1} was noted for both steroids. Brain concentrations were low at low infusion rates, indicating that acute tolerance was not occurring. Significant positive correlations were noted between dose rate and serum concentrations of allopregnanolone ($r = 0.94$, $P<0.001$) and pregnanolone ($r = 0.88$, $P<0.001$). Such correlations were also seen in striatum, cerebellum, cortex and muscle for both steroids ($P<0.01$). Despite changing infusion rates, the concentrations of both steroids in brainstem, hippocampus and fat remained stable. Because no correlation between infusion rate and steroid concentration was noted in the brainstem and hippocampus, these two brain areas may be regarded as primary sites of action for allopregnanolone and pregnanolone. Pregnanolone concentrations in the brainstem and hippocampus were significantly higher than those of allopregnanolone, suggesting that allopregnanolone was more potent than pregnanolone in inducing anaesthesia.

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The major ring-A-reduced metabolites of progesterone, allopregnanolone (3α-hydroxy-5α-pregnane-20-one) and pregnanolone (3α-hydroxy-5β-pregnane-20-one) are barbiturate-like anaesthetics whose site of action is the $GABA_A$ receptor.[1 2] They are the most potent naturally occurring anaesthetics tested so far in both animals and humans.[3 4] When tested with an i.v. EEG threshold method in male rats,[3] the anaesthetic potencies of allopregnanolone and pregnanolone are greater than those of other i.v. anaesthetics that are or have been used in the clinic (Table 2).

In an earlier study,[5] we found that the overall brain concentrations of allopregnanolone at induction of anaesthesia were significantly increased in spite of the observation that the threshold dose did not differ when the infusion rate was increased from 2.0 to 3.0 mg kg^{-1} min^{-1}. Similarly, a significant increase in brain concentration (decrease in brain sensitivity) in relation to increased infusion rate has also been observed earlier with thiobutabarbital and butabarbital.[6] Earlier results with hexobarbital indicated that a criterion of critical brain areas with respect to induction of anaesthesia should be no change in active drug concentration with changing infusion rate.[6] However, an increase in hexobarbital concentration occurred in all brain areas at a slow infusion rate, indicating a decrease in brain sensitivity. This was a sign of acute tolerance to hexobarbital, as higher brain concentrations were needed to induce anaesthesia when a longer infusion time was used.[7]

Acute tolerance is the induction of functional tolerance, i.e. altered sensitivity to a drug, within the duration of a single continuous exposure to a drug.[8] Since it was first investigated,[9] the interest in acute tolerance has focused on ethanol.[10–13] However, it has also been described for many classes of general anaesthetics, including barbiturates,[14] volatile anaesthetics[15] and benzodiazeines.[16] Several neuro-

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transmitter systems, such as dopamine,[17] noradrenaline,[17] 5-hydroxytryptamine,[17] acetylcholine,[13] GABA[18] and NMDA,[19] have been implicated directly or indirectly in the development of acute tolerance. This makes it uncertain whether acute tolerance to depressant drugs in the central nervous system (CNS) is an entity with a single common mechanism. Furthermore, the development of acute tolerance varied greatly among different brain structures[10] depending on the test system used[11 12] and the age of the experimental animals.[20]

A simple method of investigating the development of acute tolerance to i.v. anaesthetics is to increase the duration of induction by changing the rate of infusion of the drug. Acute tolerance is revealed by comparing drug concentrations in the brain at the occurrence of a defined criterion of anaesthesia. In the present study, we used brain concentrations of allopregnanolone and pregnanolone at the time of an EEG end-point induced at different rates as a measure of CNS sensitivity.[14] This design also made it possible to compare the pharmacodynamic properties of allopregnanolone and pregnanolone at the induction of deep anaesthesia in male rats, and to identify the critical brain areas involved in the induction of anaesthesia with allopregnanolone and pregnanolone.

Materials and methods

Animals

The study was approved by the Regional Ethics Committee for Animal Experiments in Umeå (Umeå djuförsöksnämnd). Male adult Sprague–Dawley rats ($n = 47$) (MOL: SPDR HAN, Möllegaard, Li, Skensved, Denmark) were used in all experiments. The rats were housed at three per cage in a room with constant temperature (24°C). They had access to water and standard rat food *ad libitum*.

Drugs

Allopregnanolone (CoCensys, Irvine, CA, USA) and pregnanolone (Steraloids, Wilton, NH, USA) were dissolved in 20% 2-hydroxypropyl-β-cyclodextrin (β-cyclodextrin; Sigma, St Louis, MO, USA) at a concentration of 4.0 mg ml^{-1}. The preparations were placed in a Bransonic 2210 ultrasonic bath for approximately 15 h and agitated occasionally. All steroids were dissolved in β-cyclodextrin by visual inspection.

EEG threshold method

The anaesthetic effects of allopregnanolone and pregnanolone in the rats were determined with an i.v. EEG threshold method.[3] Allopregnanolone or pregnanolone was infused i.v. into one tail vein at a constant infusion rate, and the EEG was recorded continuously from subcutaneous stainless steel electrodes. The infusion was stopped immediately when the first burst suppression period of 1 s or more was noted in the EEG (the 'silent second', SS). As illustrated in earlier papers,[3 21] the SS is easily detected against the background of an EEG consisting mainly of high-amplitude potentials. The appearance of the SS occurs at a much deeper level of anaesthesia than the loss of the righting reflex. The time to reach the SS was recorded and the amount of steroid needed to induce the effect was calculated. This dose was considered to be the threshold dose. Data for a dose rate curve were generated by repeated determinations with different infusion rates. Allopregnanolone was infused at 1.0 ($n = 1$), 2.0 ($n = 5$), 4.0 ($n = 5$) and 8.0 ($n = 6$) mg kg^{-1} min^{-1}, and pregnanolone at 0.5 ($n = 3$), 1.0 ($n = 6$), 2.0 ($n = 6$), 4.0 ($n = 6$) and 8.0 ($n = 9$) mg kg^{-1} min^{-1}. The order of testing and dose rates were allocated at random. However, because of failure to induce anaesthesia with the lower rates (see Results, Dose rate curves for allopregnanolone and pregnanolone at induction of SS), not all rats were used. A few of the unused rats were reallocated to the highest dose rate. The infusion dose rate that gave the lowest threshold dose when drug administration was terminated at SS was defined as the optimal dose rate.[21]

Tissue sample preparation

Rats were killed by decapitation after the first SS was initiated. Trunk blood was collected and the brain was dissected immediately into the cerebellum, cortex, hippocampus, brainstem (midbrain, medulla oblongata) and striatum, largely according to Glowinski and Iversen.[22] The blood vessels on the surface of the brain hemispheres were carefully removed. A macroscopic autopsy was always carried out. Abdominal fat tissue from the retroperitoneal areas and part of the psoas muscle were removed from each rat. After weighing, the tissue was frozen at –70°C until analysis. All the samples were extracted later with 99.5% ethanol for 7 days at 4°C. Recovery of steroids in this procedure has been shown to be 100%.[23]

Celite chromatography and steroid assay

Allopregnanolone and pregnanolone in tissue and serum extracts were separated by Celite chromatography, as described by Bäckström *et al.*[24] and verified by Corpéchot *et al.*[25] The recovery rate of allopregnanolone and pregnanolone was determined in every run by using [^{3}H]allopregnanolone and [^{3}H]pregnanolone tracers. Recovery of allopregnanolone and pregnanolone was 85%. The concentrations of allopregnanolone and pregnanolone in brain tissue extracts were measured by radioimmunoassay. Radioactive steroid tracers ([9,11,12-^{3}H(N)]-5α-pregnan-3α-ol-20-one and [9,11,12-^{3}H(N)]-5β-pregnan-3α-ol-20-one) were purchased from NEN Life Science Products, Boston, MA, USA. Allopregnanolone and pregnanolone antisera were raised against 3α-hydroxy-

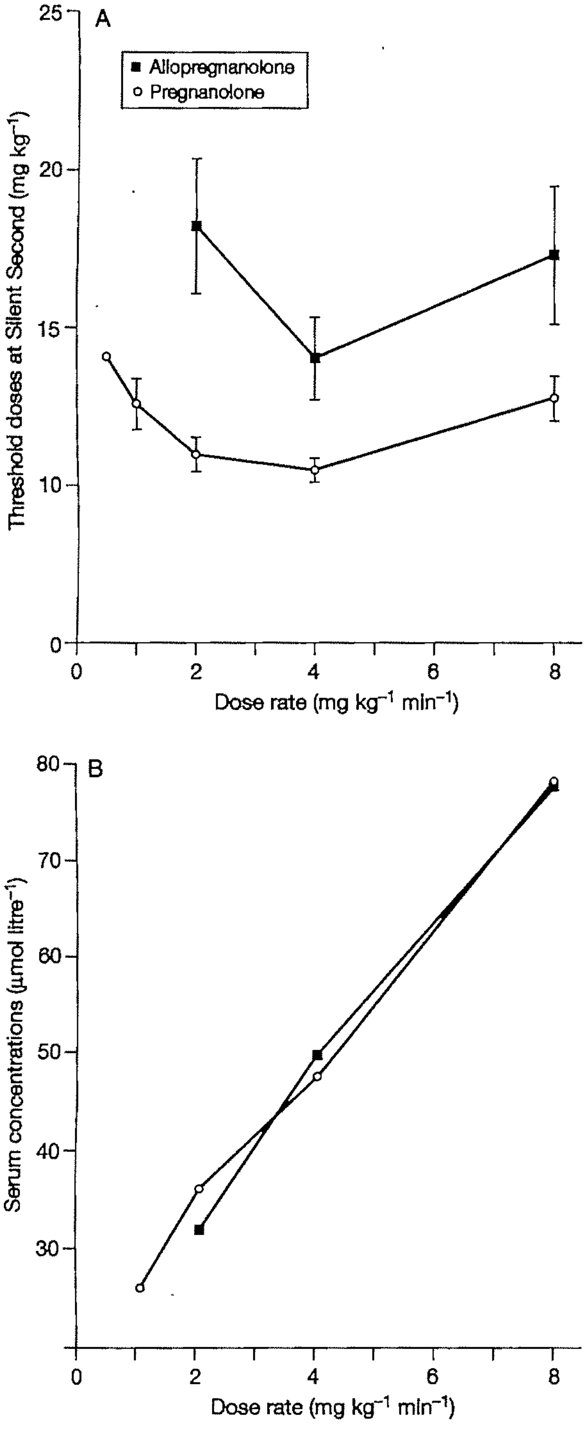

Fig 1 Relationship between infusion rates of steroid anaesthetics and corresponding threshold doses (A) and serum concentrations (B) obtained after determination of the silent second. All values are means. Bars indicate the SEM. In the pregnanolone groups n=6 except for infusion rates of 0.5 mg kg^{-1} min^{-1} (n=1) and 8 mg kg^{-1} min^{-1} (n=8). In the allopregnanolone groups n=5 except for 8 mg kg^{-1} min^{-1} (n=6).

20-oxo-5α-pregnan-11α-yl carboxymethyl ether or 3α-hydroxy-20-oxo-5β-pregnan-11α-yl carboxymethyl ether coupled to bovine serum albumin. Antiserum was kindly provided by Dr Robert Purdy (San Diego, CA, USA). Cross-reactivity has been tested earlier,[26 27] and both antisera are highly specific. The sensitivity of both assays was 25 pg, with an intra-assay coefficient of variation of 7% and an inter-assay coefficient of variation of 8%. The intra-assay coefficient of variation was calculated from duplicate values in the assay. The mean inter-assay control for pregnanolone was 20.6 nmol g^{-1} (range 18.2–26.4 nmol g^{-1}) and for allopregnanolone it was 13.1 nmol g^{-1} (range 11.2–22.5 nmol g^{-1}).

Statistical analysis

Differences in the threshold doses among dose rate groups and between allopregnanolone and pregnanolone concentrations in serum and tissue samples were assessed with the Mann–Whitney *U*-test. Parametric correlations (*r*) and regression coefficients (*b*) were used to study the relationship between infusion dose rate and steroid concentrations and the relationship between threshold doses and steroid concentrations respectively. All statistical calculations were performed using Origin version 4.1 software (Microcal Software, Northampton, MA, USA). Values of P<0.05 in a two-tailed test were taken to represent a significant difference. All results are presented as mean (SEM). The symbol n denotes the number of animals in each test.

Results

Dose rate curves for allopregnanolone and pregnanolone at induction of SS

The dose rate curve (Fig. 1A) shows the dose for SS plotted against the infusion rate for allopregnanolone and pregnanolone. A V-shaped curve was obtained for both steroids. For both curves, an optimal infusion rate of 4.0 mg kg^{-1} min^{-1} was found which gave the lowest dose of allopregnanolone or pregnanolone needed to obtain an SS (i.e. the threshold dose). The corresponding optimal threshold doses were 14.05 (1.32) mg kg^{-1} for allopregnanolone and 10.46 (0.37) mg kg^{-1} for pregnanolone. The threshold doses of pregnanolone were significantly lower than those of allopregnanolone at the infusion rates of 2.0, 4.0 and 8.0 mg kg^{-1} min^{-1} (P<0.001, Mann–Whitney *U*-test).

In one rat tested with allopregnanolone at 1.0 mg kg^{-1} min^{-1}, no SS was obtained after 29.5 min of infusion, when a dose of 29.5 mg kg^{-1} had been injected. Among the three rats tested with pregnanolone at 0.5 mg kg^{-1} min^{-1}, SS was obtained in only one rat; for the other two rats, the infusion was stopped after 50 min, when a dose of 25 mg kg^{-1} pregnanolone had been injected, with no sign of an SS in the EEG. Results from one rat that received pregnanolone 8.0 mg kg^{-1} min^{-1} were excluded because of changes in the lungs.

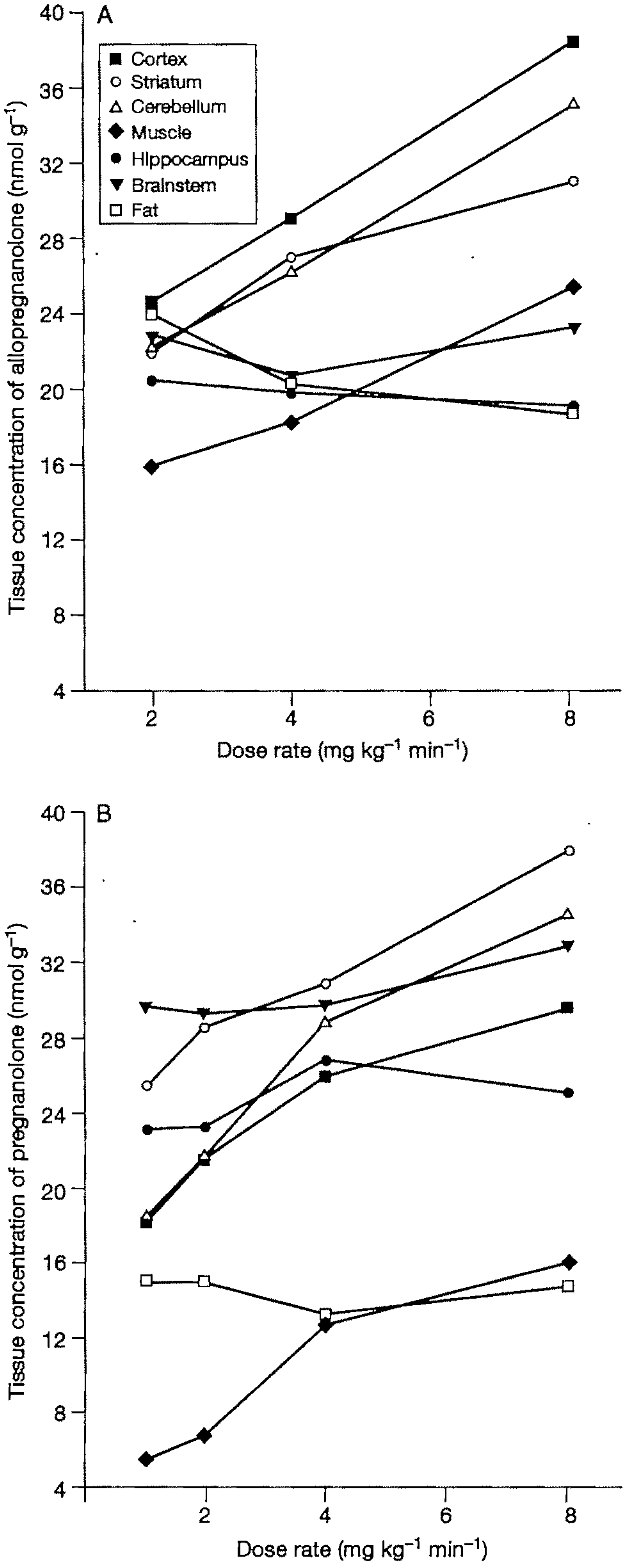

Fig 2 Relationship between infusion rate and tissue concentrations for allopregnanolone (A) and pregnanolone (B). Numbers of experimental animals in the different groups are as given in Fig. 1.

Relationship between dose rate and steroid concentration

Serum concentrations of allopregnanolone and pregnanolone plotted against dose rate are shown in Fig. 1B. A significant linear increase in serum concentrations with increasing infusion rate was noted for allopregnanolone [$b = 7.55$, $r = 0.94$, df (degrees of freedom) = 14, $P<0.001$] and pregnanolone ($b = 7.33$, $r = 0.88$, df = 24, $P<0.001$). Although the threshold doses for allopregnanolone at induction of SS were significantly higher than for pregnanolone (Fig. 1A), the average serum concentrations of the two steroids were not significantly different at any of the infusion rates tested.

The relationships between dose rate and tissue concentration at SS are shown in Fig. 2A and B for allopregnanolone and pregnanolone respectively. For allopregnanolone, cortex ($b = 2.3$, $r = 0.77$, df = 14, $P = 0.001$), striatum ($b = 1.44$, $r = 0.60$, df = 14, $P = 0.014$), cerebellum ($b = 2.16$, $r = 0.75$, df = 14, $P = 0.001$) and muscle ($b = 1.64$, $r = 0.71$, df = 14, $P = 0.002$) showed significantly increased steroid concentration at SS with increasing infusion rate (Fig. 2A). However, the allopregnanolone concentrations in brainstem, hippocampus and fat did not change significantly with infusion rate.

Tissue concentrations of pregnanolone at SS showed essentially the same pattern as those of allopregnanolone when plotted against dose rate (Fig. 2B). A significant increase in pregnanolone concentration with increasing infusion rate was noted in cortex ($b = 1.53$, $r = 0.68$, df = 24, $P<0.001$), striatum ($b = 1.63$, $r = 0.63$, df = 24, $P = 0.001$), cerebellum ($b = 2.22$, $r = 0.65$, df = 24, $P<0.001$) and muscle ($b = 1.53$, $r = 0.69$, df = 24, $P<0.001$). No significant change in pregnanolone concentration in relation to increasing infusion rate was noted in brainstem, hippocampus and fat. These results indicated that allopregnanolone and pregnanolone concentrations increased in the cortex, striatum and cerebellum with increasing infusion rate. However, no changes in steroid concentrations in brainstem and hippocampus occurred at SS in relation to dose rate. As no changes in active drug concentrations were expected at the primary sites of action in the brain, the brainstem and hippocampus can be considered to be the primary sites of action with respect to allopregnanolone and pregnanolone in male rats.

Relationship between threshold dose and tissue concentration

The relationships between threshold dose and steroid concentration in different tissues were assessed by linear regression. In the analysis of allopregnanolone, no significant relationship was found for serum, muscle, cortex, striatum, cerebellum and hippocampus. A significant relationship was found for brainstem ($b = 0.90$, $r = 0.57$, df = 14, $P<0.05$) (Fig. 3A) and fat ($b = 1.31$,

$r = 0.75$, df = 14, $P < 0.001$) (Fig. 3B). The analysis for pregnanolone gave similar results. No significant relationship was noted between threshold dose and steroid concentration in serum, muscle, cortex, striatum, cerebellum and hippocampus, whereas a significant correlation was found for brainstem ($b = 1.29$, $r = 0.52$, df = 24, $P = 0.001$) (Fig. 3C) and fat ($b = 1.21$, $r = 0.45$, df = 24, $P<0.05$) (Fig. 3D). These findings indicate that the brainstem has a different role in the generation of anaesthesia in comparison with the hippocampus. Fat turns out to be a special tissue that handles allopregnanolone and pregnanolone actively, in a similar way to the brainstem.

Comparison of steroid concentrations in brainstem and hippocampus

As our results revealed that steroid concentrations in the brainstem and hippocampus did not change significantly with infusion rate, we used these two brain areas to determine the anaesthetic potencies of allopregnanolone and pregnanolone by comparing the steroid concentrations in these two brain areas (Table 1). Comparison of the active drug concentrations in the brain areas involved critically in the induction of SS is more informative than comparison of the threshold doses at SS, because the former eliminates the pharmacokinetic factors involved in the infusion of the drug.

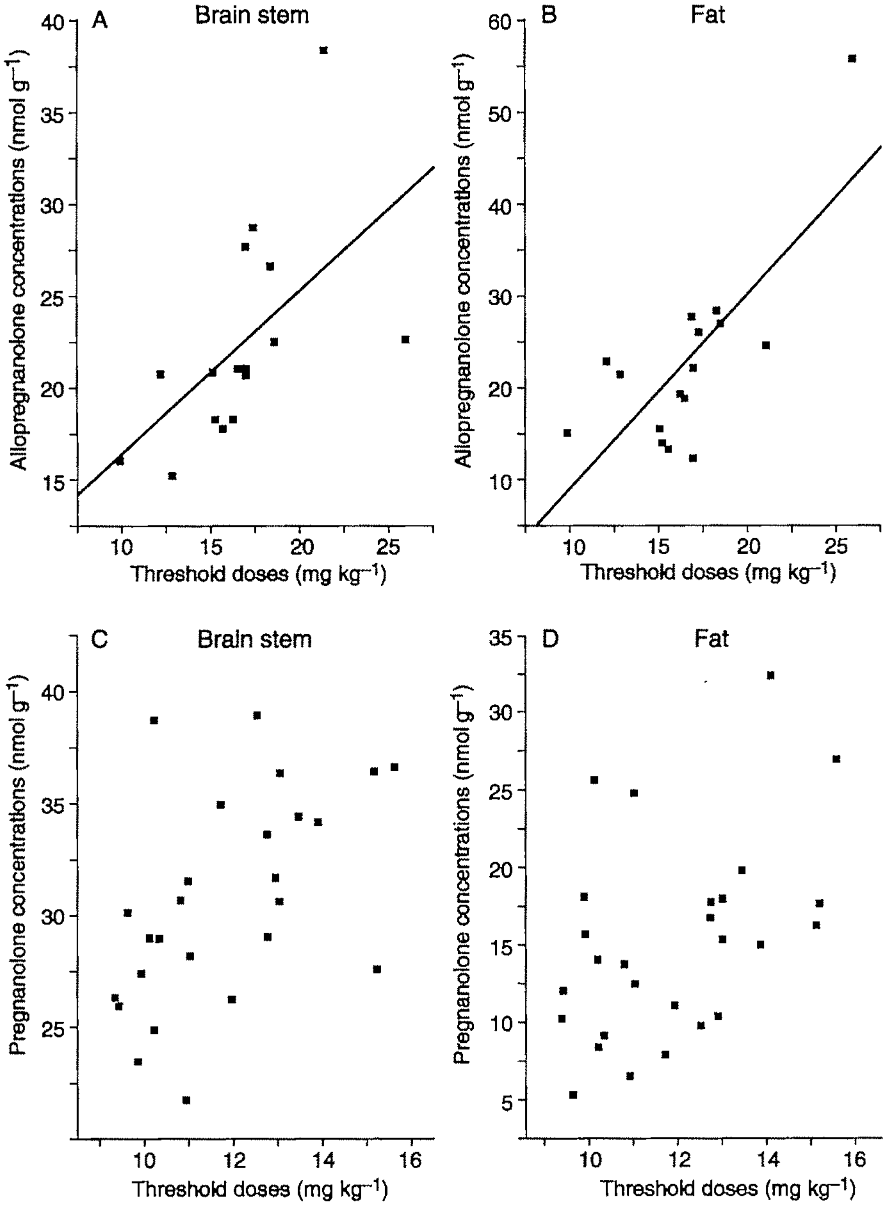

Fig 3 Relationship between threshold doses of allopregnanolone and concentrations in brainstem (A) and fat (B) obtained at the silent second. Relationship between threshold doses of pregnanolone and concentrations in brainstem (C) and fat (D) obtained at the silent second.

Table 1 Tissue concentrations of allopregnanolone and pregnanolone. Data are mean (SEM). NS=not significant

Infusion rate (mg kg^{-1} min^{-1})	**Allopregnanolone** (nmol g^{-1})	**Pregnanolone** (nmol g^{-1})	P
Brainstem			
2.0	22.78 (2.35)	29.34 (2.04)	<0.001
4.0	20.71 (1.96)	29.88 (1.94)	<0.001
8.0	23.18 (3.13)	33.06 (1.78)	<0.001
Average	22.28 (1.44)	30.71 (0.92)	<0.001
Hippocampus			
2.0	20.47 (1.50)	23.40 (1.81)	NS
4.0	19.71 (1.15)	26.95 (1.40)	<0.05
8.0	19.02 (1.25)	25.26 (1.67)	<0.05
Average	19.69 (0.72)	24.76 (0.83)	<0.001
Fat			
2.0	23.96 (2.63)	15.23 (2.29)	<0.05
4.0	20.33 (2.36)	13.36 (2.54)	NS
8.0	18.59 (2.56)	14.98 (2.68)	NS
Average	23.03 (2.59)	14.57 (1.42)	<0.005

We found that pregnanolone concentration in the brainstem was significantly higher than the allopregnanolone concentration at the infusion rates of 2.0, 4.0 and 8.0 mg kg^{-1} min^{-1} ($P<0.001$, Mann–Whitney *U*-test). The average pregnanolone concentration when all infusion rates were pooled was also significantly higher than that of allopregnanolone ($P<0.001$). In the hippocampus, the pregnanolone concentration at the infusion rate of 2.0 mg kg^{-1} min^{-1} was not significantly different from the corresponding allopregnanolone concentration, while the pregnanolone concentrations at the infusion rates of 4.0 and 8.0 mg kg^{-1} min^{-1} were significantly higher than the corresponding allopregnanolone concentrations ($P<0.05$ for both infusion rates). When all infusion rates were pooled, the average pregnanolone concentration in hippocampus was significantly higher than that of allopregnanolone ($P<0.001$). A similar difference was seen in fat when all infusion rates were pooled (Table 1).

Relationship between serum and tissue concentrations

Data on serum concentrations are given in Fig. 1B; data on tissue concentrations of allopregnanolone are given in Fig. 2A and those of pregnanolone are given in Fig. 2B. Dose rate was used as the independent variable in both sets of data, and for both steroids there was a strong positive correlation with serum concentration (Fig. 1B). In some but not all tissues (Fig. 2A and B), positive correlations were also recorded. In these tissues, positive correlations with serum concentrations were expected. We found that the steroid concentrations in serum and muscle were significantly correlated for both allopregnanolone and pregnanolone (allopregnanolone, $b = 0.18$, $r = 0.68$, $df = 14$, $P = 0.004$; pregnanolone, $b = 0.16$, $r = 0.59$, $df = 24$, $P = 0.001$), while the correlation between serum and fat was not significant for any of the steroids. Serum concentrations of allopregnanolone were also correlated significantly with concentrations in striatum ($b = 0.22$, $r = 0.75$, $df = 14$, $P = 0.001$), cerebellum ($b = 0.26$, $r = 0.72$, $df = 14$, $P = 0.002$) and cortex ($b = 0.27$, $r = 0.73$, $df = 14$, $P = 0.001$). Serum concentrations of pregnanolone were significantly correlated with concentrations in striatum ($b = 0.18$, $r = 0.57$, $df = 24$, $P = 0.002$), cerebellum ($b = 0.28$, $r = 0.69$, $df = 24$, $P<0.001$) and cortex ($b = 0.18$, $r = 0.68$, $df = 24$, $P<0.001$).

Discussion

Sixty years ago, Selye[28] first reported the sedative—anaesthetic activities of progesterone and deoxycorticosterone and identified their ring-A-reduced metabolites as extremely potent sedative–hypnotic agents. Selye's initial observations on the anaesthetic effects of steroids, particularly the 3α-hydroxy ring-A-reduced metabolites of progesterone, prompted the development of a class of steroid anaesthetics that culminated in the introduction of several of them into clinical practice.[2 29] The rapid onset of their behavioural effects precludes a non-genomic mechanism of action for such steroids. However, it was not until Harrison and Simmonds[30] demonstrated in 1984 that a steroid anaesthetic, alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione), selectively enhanced the interaction of GABA with the GABA$_A$ receptor, that a protein-founded mechanism to explain the behavioural effects of these compounds emerged. The natural 3α-hydroxy ring-A metabolites of progesterone, allopregnanolone and pregnanolone, have been shown to be the most potent GABA$_A$ receptor ligands, with affinities comparable to those of benzodiazepines and at least a thousand times greater than that of the barbiturate pentobarbital.[2 31] As for hexobarbital and thiopental, an increase in the sensitivity of the brain to allopregnanolone and pregnanolone with age has been observed.[21 32] Because of these findings, the male rats in the present study were used at the age of 65–70 days, when their anaesthetic sensitivity to allopregnanolone and pregnanolone would have stabilized.[32]

The dose rate curves obtained with allopregnanolone and pregnanolone both have the same general appearance (Fig. 1A). The appearance of the curves is also similar to that of curves obtained with different barbiturates[5 21 34] and some other i.v. anaesthetics.[35 36] A number of threshold doses at optimal rates and the slopes of the curves at infusion rates higher than the optimal rate are included in Table 2. The table shows that there is large variation in threshold dose at the corresponding optimal rates. Both steroids are potent, with low threshold doses, but the solvent has an effect. Among other drugs that have been tested, only propofol and methohexital have threshold doses at the optimal infusion rates that are within the same range as those of the steroids, but they seem to be slightly less potent.

Table 2 Doses at optimal infusion rates and slopes of the infusion rate curve at higher rates for various substances. All infusion rate curves were similar to those shown in Fig. 1A. The barbiturates were used as sodium salts. C=β-cyclodextrin; A=albumin; I=Intralipid; W=water; Rac=racemate; ND=not determined

Substance	**Dose at optimal rate [mg kg^{-1} (mmol g^{-1})]**	**Optimal infusion rate (mg kg^{-1} min^{-1})**	**Solution**	**Age (days)**	**Slope at high infusion rates (min)**	**Slope calculated at this rate interval (mg kg^{-1} min^{-1})**	**Reference**
Steroids							
Allopregnanolone	14.0 (44.0)	4	C	70	0.82	4–8	This study
Allopregnanolone	7.9 (24.8)	3	A	60	ND		5
Allopregnanolone	6.7 (21.0)	2	I	45	0.27	2–10	32
Allopregnanolone	5.1 (16.0)	2	I	110	ND		32
Pregnanolone	10.5 (33.0)	4	C	70	0.57	4–8	This study
Pregnanolone	8.9 (27.9)	2	I	50	0.34	2–10	32
Pregnanolone	6.6 (20.7)	2	I	115	0.53	2–10	32
Barbiturates							
Hexobarbital (Rac)	63.0 (243.0)	15	W	>120	0.34	15–60	21
Hexobarbital ((+)-*S*)	46.2 (178.2)	15	W	280	ND		33
Hexobarbital ((–)-*R*)	148.3 (572.0)	15	W	280	ND		33
Narcobarbital (Rac)	72.8 (223.2)	15	W	>65	0.61	15–30	34
Narcobarbital (+)	61.3 (187.9)	15	W	>65	ND		34
Narcobarbital (–)	84.5 (259.0)	15	W	>65	ND		34
Amobarbital	71.0 (284.8)	10	W	>120	1.10	10–40	21
Thiobutabarbital	79.9 (317.9)	20	W	>200	1.61	20–50	6
Pentobarbital (Rac)	56.1 (225.1)	5	W	>120	1.07	5–15	21
Thiopental (Rac)	38.3 (144.9)	10	W	>120	0.55	10–40	21
Methohexital (Rac)	13.9 (48.9)	10	W	>120	0.11	10–30	21
Miscellaneous							
Flurazepam	72.0 (185.6)	15	W	125	2.71	15–25	35
Propofol	13.4 (75.2)	10	I	90	0.34	10–20	36
Circulation time (tail to brain)	–	–	–	–	0.10	–	21

There is also a distinct difference in threshold dose between the isomers of both hexobarbital and narcobarbital, the dose of the racemate being intermediate. Furthermore, there is considerable variation in the slope of rates higher than optimal (Table 2). If only simple diffusion at the site of action were involved in this slope, i.v. anaesthetics, which are highly lipid-soluble substances, would have a slope that corresponds to the circulation time. This seems to be the case for hexobarbital, methohexital, propofol and the two steroids, when tested in young rats. All other substances had slopes above 0.5 min, and among these it has been shown that the penetrations of thiopental into the brain could be facilitated by probenecid[37] and penicillins.[38] This indicates the presence of a transport mechanism, but for thiobutabarbital[6] a change in sensitivity may also be involved. The rate curve clearly shows that, when the potencies of i.v. anaesthetics (and probably also of other substances) are compared *in vivo*, the dose obtained at the optimal infusion rate should be chosen. However, it is obvious that pharmacokinetic properties still have to be considered. The different results with different solvents in the case of steroids are only one example of remaining kinetic influences.

We found that less pregnanolone than allopregnanolone was needed to induce the SS in all comparable dose rate groups (Fig. 1A). However, serum concentrations of the two substances were almost identical (Fig. 1B). From a pharmacokinetic point of view, this indicates that there had been a rapid loss of allopregnanolone from the blood. Such a loss could be accomplished by rapid accumulation in some other tissues or by rapid metabolism of allopregnanolone. Redistribution to muscle, as proposed by Goldstein and Aronow,[39] is unlikely because no difference between pregnanolone and allopregnanolone concentrations could be established. As seen in three barbiturates,[6] fat is another alternative site of redistribution, especially after long induction times. In the present experiments there was a difference between the levels of accumulation of allopregnanolone and pregnanolone in fat (Table 1), but the difference was not large enough to explain the difference in threshold doses at SS (Fig. 2A). Furthermore, there was only a slight accumulation of allopregnanolone in fat at lower infusion rates (Fig. 2A). Such a result was unexpected and could indicate rapid loss of steroid from fat, but as not all tissues were analysed no definite conclusion can be drawn to explain the loss of allopregnanolone during infusion.

An earlier study[7] has shown that acute tolerance to hexobarbital can be induced by stable anaesthesia lasting more than 10 min. This was in the same range as the infusion time for pregnanolone at infusion rates of 0.5 and 1.0 mg kg^{-1} min^{-1} (>10 min). For allopregnanolone the infusion time used to induce the SS at an infusion rate of 2.0 mg kg^{-1} min^{-1} was about 9 min. For the rat infused with allopregnanolone at 1.0 mg kg^{-1} min^{-1}, an SS had not been obtained when the infusion time reached 29.5 min. This indicates that the increased threshold dose of allopregnanolone and pregnanolone at low infusion rates could have been a result of the development of acute tolerance. The steroid infusion time required to reach SS was within the range that caused acute tolerance to hexobarbital.[7] Analysis of hexobarbital concentrations showed an increased concentration in all brain areas studied as the infusion rate decreased,[6] which suggested decreased brain sensitivity. Such an increased concentration could be used as a direct measure of acute tolerance.[14] However, the development of acute tolerance in the allopregnanolone and pregnanolone groups was not supported by our results. Significantly lower steroid concentrations were found in cortex, striatum and cerebellum when the infusion rate was low. This is the reverse of what would have been expected if tolerance had developed. Thus, we conclude that acute tolerance did not develop to the anaesthetic effect during infusions of allopregnanolone and pregnanolone lasting 10 min or less.

Analysis of allopregnanolone and pregnanolone in all brain areas revealed that the brain had similar sensitivity to the two steroids. Despite the observation of a significant increase in steroid concentrations in cortex, striatum and cerebellum as the infusion rate was increased, the steroid concentrations in brainstem and hippocampus remained unchanged (Fig. 2). This finding indicated that anaesthetic sensitivity to allopregnanolone and pregnanolone in the brainstem and hippocampus was stable and independent of the changes in infusion rates and serum steroid concentrations. As we were using a threshold technique with a defined criterion recorded directly from the brain—a criterion that was reached with all dose rates and that was also used to terminate the infusion—this is the expected result. Our earlier results with hexobarbital indicated that critical brain areas with respect to induction of anaesthesia could be defined as areas with no change in active drug concentrations that depended on the infusion rate.[6] Using this definition, cortex, striatum and cerebellum were excluded as the primary site of action with respect to allopregnanolone- or pregnanolone-induced anaesthesia. Thus, the remaining brain areas—the brainstem and hippocampus—may be considered as the primary sites of action for both steroids.

The brainstem was also distinguished as the only part of the brain that retained a relationship between threshold dose and tissue concentration. For both steroids, the relationship was recorded as a weak but significant correlation (Fig. 3A and C). Because the threshold technique depends on a simple feedback system, a strong correlation founded on a direct relationship is to be expected from a methodological point of view. However a comparison of the dose rate curves (Fig. 1A) with the corresponding serum concentrations (Fig. 1B) points to complex pharmacokinetics. When the infusion rate is increased, higher serum concentrations are needed to reach the concentration in the brainstem found at SS. This is best illustrated by the quotient between concentrations in the brainstem and serum. With allopregnanolone the quotient was 0.78 (0.13) at the infusion rate of 2.0 mg kg^{-1} min^{-1} and 0.30 (0.04) at the rate of 8.0 mg kg^{-1} min^{-1}. The corresponding values with pregnanolone were 0.82 (0.07) and 0.45 (0.05). Despite this altered penetration, a weak correlation between threshold dose and tissue concentration was still present when the brainstem was the target organ (Fig. 3A and C). Instead of a direct, strong relationship, only around 30% of the variability of the concentration in the brainstem was explained by the dose, but as it was the only correlation found in the parts of the brain that were analysed, this strengthens the possibility that the brainstem has a critical function in the induction of the SS.

In the present study, a linear correlation between threshold dose and the concentration in fat at SS was observed for both allopregnanolone and pregnanolone (Fig. 3B and D). No significant correlation between threshold dose and muscle concentration was observed. When we studied the tissue concentrations in different compartments, we found that the steroid concentrations in serum and muscle were significantly correlated for both allopregnanolone and pregnanolone, while the correlation between serum and fat was not significant for any of the steroids. This suggests that the muscle compartment was involved in the rapid distribution of steroid. However, fat could be regarded as a special tissue that actively processes allopregnanolone and pregnanolone in a similar way to the brainstem, because a significant linear correlation between threshold dose and tissue concentration of both steroids was found only for brainstem and fat (Fig. 3).

As discussed by Bolander *et al.*,[21] the threshold dose at the optimal dose rate could be used as a comparable measure of the potency of allopregnanolone and pregnanolone in adult animals. When the threshold doses of two steroid anaesthetics were compared, we found that the threshold doses of allopregnanolone were significantly higher than the corresponding threshold doses of pregnanolone at SS. This was at variance with a previous study using Intralipid® as the steroid solvent, in which the average threshold dose for allopregnanolone was significantly lower than that of pregnanolone at SS in both young and adult rats.[32] However, serum concentrations of allopregnanolone and pregnanolone in the present study were not significantly different from each other (Fig. 1). Since the anaesthetic sensitivity in rat brainstem and hippocampus remained stable as the infusion rate was increased, we tentatively considered these two brain areas as the primary sites of action and compared the steroid concentrations in the two brain areas. Allopregnanolone concentrations in the brainstem and hippocampus were generally lower than those of pregnanolone (Table 1), suggesting that allopregnanolone was more potent than pregnanolone in inducing anaesthesia. Results from the present study indicate that the active drug concentrations at the primary sites of action are in agreement with previous findings.[32] Our different results with regard to threshold doses could have been due to the steroid solvent we used, β-cyclodextrin in place of Intralipid®. This indicates that i.v. cyclodextrin solution could alter the pharmacokinetic properties and clinical behaviour of concurrently administered CNS depressant agents, and results obtained with cyclodextrin as a solvent must be evaluated carefully.

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REVIEW ARTICLE

Codeine phosphate in paediatric medicine

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Codeine is an old drug that still enjoys widespread clinical use although the logical basis for its popularity has been questioned.[66] It is considered to be suitable for mild to moderate pain but not for more intense pain even in large doses.[94] The World Health Organisation has devised a three-step analgesic ladder for the progressive treatment of increasing pain; on this codeine is considered a weak opioid and occupies a position on the second step (Fig. 1).[113] A significant degree of unpredictable, variable or poor response to treatment with codeine has been reported in many human and animal studies. Indeed, some single dose studies in adults, have shown no difference between codeine and placebo,[54 60] and a quantitative systemic review suggests that codeine 60 mg has a number needed to treat (NNT) of 18 which is very high when compared with 5.0 for paracetamol 600 mg and 3.1 for the combination.[78]

Codeine is frequently recommended for paediatric use.[2 37 100] A recent survey of paediatric anaesthetists in the UK showed that alongside morphine and fentanyl, codeine is the most widely prescribed opioid analgesic in paediatric anaesthetic practice.[34] The reputedly lower incidence of opioid-related side effects has made codeine popular for the younger age groups including neonates and especially in situations where airway management and neurological assessment are critical.[56 69 102 106] These suggested benefits have been noted after single doses although they may not exist when repeated doses are used.[69] In fact, few clinical studies of the analgesic efficacy or side effects of codeine in children have been undertaken, and although the incidence of side effects may be low, analgesia may be inadequate for post-operative pain in some circumstances.[102] Pain assessment is difficult in paediatric populations especially neonates and preverbal children and this complicates both the study and use of analgesics particularly those with low efficacy or unpredictable effects. Significant variability in both the pharmacokinetics and pharmacodynamics of codeine has been shown in animal and adult human laboratory experimental studies.[24 25 38 74 105 112 115] In this review we shall examine the reasons for this variability and unpredictability in the effects of codeine in both laboratory and clinical investigations and assess evidence for its suitability for use in preverbal infants and children.

Pharmacology of codeine[37 40]

Codeine (Fig. 2) is a naturally occurring opium alkaloid: 7,8-didehydro-4,5-epoxy-3-methoxy-*17*-methyl-morphinan-6-ol monohydrate.[1] Like morphine it is a constituent of the opium poppy, *Papaver somniferum*. It was isolated from opium in 1833 by Robiquet and its pain-relieving effects were recognized shortly after. Codeine constitutes about 0.5% of opium, which continues to be a useful source of its production, although the bulk of codeine used medicinally is prepared by the methylation of morphine. Codeine is less potent than morphine, with a potency ratio of 1:10.[111]

Dosage and uses

Codeine can be given by the oral, rectal and intramuscular (i.m.) routes. The intravenous (i.v.) route is not recommended because of dangerous hypotensive effects probably

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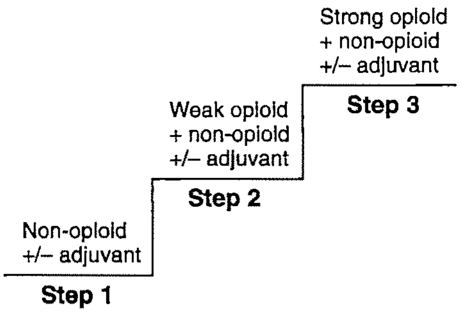

Fig 1 World Health Organization analgesic ladder.

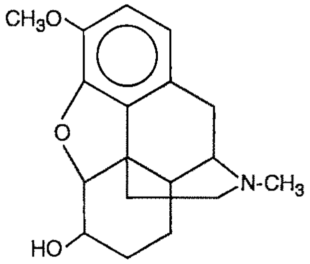

Fig 2 The chemical structure of codeine.

related to histamine release.[85] In children, it is generally given in doses of 1 mg kg^{-1} up to a maximum of 3 mg kg^{-1}day^{-1}; however, larger doses have been used.[3,102] Codeine is often used in combination with other drugs, for example aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and diphenhydramine in the treatment of mild to moderate pain. In neonates and children it has been used in both acute and chronic painful conditions and particularly for post-operative and cancer pain.[34,51,55,69,100] Its antitussive and constipating properties also mean that it is used in many cough, cold and antidiarrhoeal remedies.

Pharmacokinetics

The vast majority of pharmacokinetic data for codeine has been obtained from investigations in adults. Very little information is available from studies in children or infants and to our knowledge there is no published work in neonates.

Codeine is rapidly, and well absorbed following oral administration, approximately 50% undergoing pre-systemic metabolism in the gut and liver. Peak plasma concentration occurs after approximately 1 h and the plasma half-life is 3–3.5 h. Absorption is faster after i.m. injection, the time to peak plasma concentration is about 0.5 h. The volume of distribution is 3.6 litre kg^{-1} and the clearance is 0.85 litre min^{-1}.[37] Rectal codeine has been recently introduced into paediatric practice. A study in healthy adult volunteers showed no difference in codeine bioavailability following rectal or oral administration with a systemic availability of about 90%.[77] In the post-operative period these values may be less predictable; in one study clearance varied 4-fold and systemic availability after oral dosage was between 12 and 84%.[86]

Available research findings imply that age specific differences in the pharmacokinetics of codeine may be significant. In a comparison of i.m. and rectal codeine in children aged 3 months to 12 yr for post-operative analgesia, peak plasma levels of codeine were achieved as expected between 30 and 60 min in both groups but rectal bioavailability was found to be lower.[72] In another study of rectal codeine for post-operative analgesia in infants and children aged between 6 months and 4 yr, the mean initial half-life was 2.6 h, but in the infants of the lowest body weight, the half life was over 2 h longer than this mean value.[92] In addition, plasma drug concentration data indicate that a rectal dose of codeine of 0.5 mg kg^{-1} in children can result in similar, or slightly greater, plasma concentrations of codeine and its metabolites than after 60 mg orally in adults.[89] More information is clearly required, particularly for neonates and in the post-operative setting in order to understand fully the effects of development on codeine pharmacokinetics in clinical situations.

Metabolism[37]

Codeine is principally metabolized in the liver in one of three ways: glucuronidation at the 6-OH position, the principal route; *N*-demethylation to norcodeine (10–20%); and *O*-demethylation to morphine (5–15%). Between 5 and 15% of the drug is excreted unchanged in the urine (Fig. 3). Other minor metabolites, normorphine and hydrocodone, have also been identified.[1]

In 1948, Sanfilippo first suggested that the analgesic effect of codeine was because of the proportion of the drug metabolized to morphine and this has lead to the belief that codeine is a prodrug, with morphine as its principal active metabolite and having little or no intrinsic analgesic activity of its own.[99]

The efficacy of a prodrug is dependent on the amount of active metabolite formed. Variable expression of the enzymes involved in the biotransformation of drugs can lead to substantial differences in the production rate and plasma concentration of metabolites, and hence, the efficacy of a prodrug.

It has been known for some time that *genetic variability* in drug metabolism is an important cause of inter-individual variations in drug efficacy and maturation of enzyme systems is another important factor for certain compounds. O-Demethylation of codeine to morphine is dependent on the cytochrome P450 enzyme, CYP2D6, which is known to show genetic polymorphism,[23,32,116] whereas the other metabolic pathways for codeine are not dependent on this enzyme. *N*-Demethylation for example is catalysed by CYP3A, another P450 enzyme.[52,114]

A large number of different genetic variants are known to exist for CYP2D6, which leads to a wide spectrum of metabolic capabilities within study populations.[31,71] When

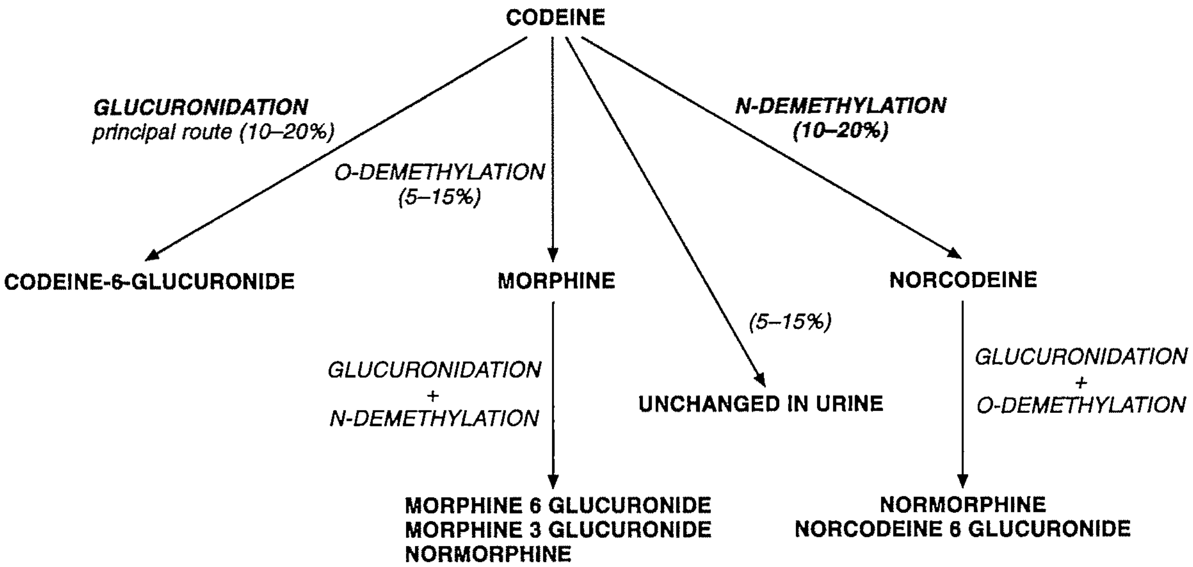

Fig 3 Metabolism of codeine.

discussing these differences, individuals are normally classified as either poor metabolizers (PM) or extensive metabolizers (EM) depending on the activity of the enzyme, although this is known to be an oversimplification (see below).[45 53 61 120] Poor metabolizers will produce little or no morphine from codeine whereas extensive metabolizers will produce significant amounts of morphine although the actual amount produced may show wide variation.[42 95 105] The metabolic differences between PMs and EMs are known to remain constant even after chronic codeine dosing.[24 115]

Despite the popularity of codeine in paediatric practice, the influence of development on the efficacy and side effects of codeine has not been well investigated. It has been suggested that infants and neonates have a reduced metabolic capacity for codeine.[92] CYP2D6 activity is absent or less than 1% of adult values in fetal liver microsomes. *O*-Demethylation of codeine to morphine does not occur *in utero* but activity of the enzyme is known to increase markedly immediately after birth regardless of gestational age. This increase in enzyme activity is maintained, although it may still be below 25% of adult values before 5 yr old. The efficiency of the enzyme to carry out the *O*-demethylation reaction also appears to be much lower in neonates than in adults. The glucuronidation pathway is also immature at birth and it has been shown that it continues to develop after the neonatal period. In contrast, *N*-demethylation has been found to be equivalent to that in adults at all pre- and post-natal ages.[59 64 65 73 108]

CYP2D6[4 57]

Humans have approximately 60 unique P450 genes, although only half a dozen, including CYP2D6, are responsible for the metabolism of the vast majority of the 'over the counter' and prescribed drugs. CYP2D6 is usually considered to be a hepatic enzyme but it is probably present in other organs and tissues, and has been identified in rat and canine brain tissue.[43 68 83 110] It has also been identified in human brain preparations.[8]

Unlike the majority of the other P450 genes CYP2D6 is not inducible, although there is growing evidence associating the enzyme with a number of disease states. Enhanced activity has been associated with malignancies of the bladder, liver, pharynx, stomach and, particularly, cigarette smoking related lung cancer. There has also been a link with chronic inflammatory diseases, such as rheumatoid arthritis and ankylosing spondylitis, and neurodegenerative disorders.[17 18 67 71 96] Enhanced CYP2D6 mediated metabolism of one or more dietary/environmental agents may form a reactive intermediate that plays a role in cancer initiation and/or promotion in various tissues.[80] Reduced enzyme activity is thought to be associated with an increased risk of Parkinson disease.[5]

CYP2D6 polymorphism is responsible for variation in spartine/debrisoquine oxidation. This particular oxidative step is important in the metabolism of more than 30 drugs and environmental chemicals, including about 20% of commonly prescribed drugs, for example tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), some neuroleptics, some antiarrhythmics and β-adrenoreceptor blockers as well as codeine and tramadol.[15 16]

The gene subfamily has been mapped to chromosome 22 at 22q13.1 and shows autosomal recessive inheritance. CYP2D6 activity ranges from complete deficiency to ultrafast metabolism, depending on which genetic variant is present.[47] To date, 55 variants have been identified and classified.[31 71] Most are rare with 87% of genotypes being accounted for by five different variants in the populations studied.[71 98] Classification of individuals as PMs or EMs correlates with the genetic variant expressed and the presence of activity altering mutations in the gene.[45 53 61 120] This is done by either phenotyping, using sparteine, debrisoquine or dextromethorphan as the probe drug, or by genotyping, using DNA extracted from leucocytes for a polymerase chain reaction (PCR) DNA test.[39 41 101]

Misclassification can occur in the presence of drugs that are inhibitors of CYP2D6, for example quinidine, metoclopramide, some neuroleptics, some SSRIs and some antiarrhythmics.[15 16] This is commonly because of the competitive inhibition of codeine metabolism as it has a relatively low affinity for the enzyme compared with these other compounds.

The estimated frequency of PMs in the UK is about 9%. However, there is wide variation among ethnic groups, from about 1% in Arabs to 30% in Hong Kong Chinese.[41 62 121] Caucasians have an incidence of about 7%.[9 97] The frequency of ultra-rapid EMs, a subgroup of EMs who are able to metabolize CYP2D6 substrates relatively quickly, also shows ethnic variation from 29% in Ethiopia to 1% in Swedish, German and Chinese populations.[6] In addition, variability occurs within genotypes; studies comparing Chinese and Caucasian EMs have shown differences in the pharmacokinetics of codeine.[14 117 119] This has been confirmed in investigations of other population genotypes.[109 118]

Pharmacodynamics

Mechanism of action

Potentially codeine could act via a number of different mechanisms. It may have a direct (opioid or non-opioid receptor mediated) analgesic effect or, as already mentioned, may act through metabolism to morphine or other active metabolites. Codeine binds to the μ receptor like morphine but with a much lower affinity.[22 82 93] It also binds to the κ and δ receptors but again has a much lower affinity than morphine, though the difference is less marked.[82 93] The affinities of the metabolites codeine-6-glucuronide and norcodeine to the μ receptor are similarly low.[58] Early animal studies produced conflicting results; morphine tolerant mice were found to be less tolerant of codeine and the analgesic effect of codeine is less easily reversed by naloxone than that of morphine.[7 81] Although, in a rat model significant analgesia was demonstrated only in those animals able to metabolize codeine to morphine.[25]

Further attempts to elucidate the mechanism of action of codeine used adult human experimental models to compare the effect of codeine on *phasic* and *tonic* pain. Phasic pain is a result of a stimulus of varying intensity, analogous to pain with movement, which is known to respond poorly to opioids. Tonic pain is a result of a constant intensity stimulus and is analogous to rest pain and is opioid sensitive.[11 26 40]

Codeine was shown to have no effect on opioid-insensitive phasic pain in either extensive or poor metabolizers in these studies, which suggests that an opioid receptor mediated effect for codeine is likely.[87] Results from this study also showed that EMs but not PMs, had a good response for tonic pain, suggesting that in man codeine analgesia is both an opioid effect and that the formation of morphine is an important factor.[87] Confirmatory evidence for the dominant role of morphine in the effects of codeine in man have been obtained by competitive inhibition of codeine *O*-demethylation using quinidine.[32 33 36 103] The results from these studies show that codeine analgesia in extensive metabolizers could be blocked by pretreatment with quinidine. Studies in (adult human) volunteers using the same technique have shown that the incidence and magnitude of respiratory, pupillary and psychomotor effects are also dependent on codeine metabolism to morphine.[19 20]

Recently no analgesia from codeine was demonstrated in PM groups, even at high doses.[38 87] However in EM groups in these studies, analgesia was found to be slightly greater following codeine than with a dose of morphine producing similar plasma levels of morphine.[38 87] Although this work provides strong evidence for the dominant role of morphine in codeine analgesia, the slightly increased efficacy of codeine at similar plasma levels of morphine must be explained.

It is possible that other metabolites are responsible; there may be a pharmacokinetic mechanism or there may be a small direct analgesic effect of codeine itself. A recent study using a rat animal model has shown that hydrocodone, a possible minor codeine metabolite, has analgesic properties that are independent of its *O*-demethylated metabolite hydromorphone.[107] However, the lack of analgesic effect consistently seen in poor metabolizers makes both this mechanism and a direct effect of codeine itself unlikely.

Another explanation may be that the rapid penetration of the blood–brain barrier (BBB) by codeine and expression of CYP2D6 in the brain lead to higher levels of morphine in the central nervous system (CNS). Codeine is known to penetrate the BBB more rapidly than morphine,[84] and the presence of CYP2D6 in the CNS allows local tissue *O*-demethylation of codeine to morphine. This has been shown to be possible in rat brain homogenates and the presence of CYP2D6 has been demonstrated in both human and animal brain tissue.[8 21 43 68 83 110] Demonstration of a direct correlation between analgesia and plasma levels of morphine or its metabolites have proved to be elusive and studies difficult to interpret, particularly in children.[29 70 76 79]

Clinical efficacy

Both adult and paediatric clinical studies have demonstrated that the efficacy of codeine is low and that it has a ceiling effect at higher doses above which there is a marked increase in the incidence of side-effects.[69 72 86 91 102 104] Two recent systematic reviews have shown a small but

Table 1 Side effects of codeine

Respiratory depression
Sedation
Nausea and vomiting
Decreased gastric motility
Miosis
Dependence, though this is markedly less than with morphine
Large doses cause excitation rather than mood depression
Hypotension when given by the i.v. route[85]

significant benefit of adding codeine 60 mg to paracetamol in adults.[35, 78] Many other studies, also in adults, confirm that codeine 30–60 mg can add significantly to the analgesic effect of drugs such as aspirin, paracetamol and NSAIDs.[10, 27, 28, 44, 48, 63, 90] This additive effect is especially prominent after repeated doses, and accumulation of morphine has been suggested as an explanation.[46, 90]

Unfortunately, there have been very few clinical studies investigating the analgesic efficacy of codeine in which genetic variation is taken into consideration, and none in paediatric groups. In the only study of post-operative patients to consider this factor, the analgesic efficacy of codeine was found to be low but overall there was no difference in efficacy between the two phenotypes.[88] However, the number of PMs was very small and the overall efficacy of codeine was low throughout the study. In addition, amongst the EMs there was a very wide spectrum of metabolic ability and patients with higher concentrations of morphine and morphine-6-glucuronide had a significantly better analgesic response. Interestingly, serum concentrations of morphine and its metabolites after 1 h were much lower in the EMs in this study than those that have been generally found in healthy EM volunteers.[24, 36, 89, 103, 105, 115] This suggests that post-operative factors may significantly influence codeine metabolism, possibly leading to lower plasma concentrations of morphine and its metabolites.

Non-analgesic effects

Codeine has a side-effect profile that is broadly similar to other opioids (Table 1).

One of the reasons codeine has maintained its popularity is a reputedly lower incidence of opioid-related side effects in comparison with other drugs from this group. Codeine is commonly used for post-operative analgesia following neurosurgery because of its supposed lack of sedation, respiratory depression and the preservation of pupillary signs. A recent survey of neuroanaesthetists suggested that codeine and dihydrocodeine were the mainstays of post-operative analgesia, but in 50% of cases the same anaesthetists considered this analgesia to be inadequate. Most said they would not use morphine as an alternative for fear of side effects.[106] There is little evidence to confirm that the side effects of codeine are significantly fewer or less severe than those of other opioids at equi-analgesic doses. The antitussive and gastrointestinal effects of codeine have been found to occur at lower doses than those for analgesia, but the mechanism has not been fully elucidated.[104] Studies of gastrointestinal transit time have been largely inconclusive although in the only study to measure post-codeine morphine levels, the transit time was longer in the group who also had significantly higher plasma morphine.[49, 50, 75]

The extent to which the different non-analgesic and adverse effects of codeine can be attributed to metabolism to morphine is not known; there is increasing evidence, however, of a direct role for codeine itself. Single dose comparisons of codeine, morphine and placebo in adult volunteers have shown that at low doses side effects appear to be directly related to plasma morphine levels but that at higher doses codeine may itself be directly responsible for adverse effects.[38, 87] The importance of this finding is that, ironically, poor metabolizer groups whilst having inadequate analgesia may still experience side-effects from codeine.

Another group of patients that may experience enhanced adverse effects from codeine are the ultra-rapid extensive metabolizers. Recovery of the *O*-demethylated metabolites is much higher in the ultra-rapid EMs (15.3 *vs* 1.7–8.7% in EMs and 0.4% in PMs).[114] Thus, ultra-rapid EMs may develop increased morphine dependent effects or side effects of codeine and in addition lower than normal doses may be necessary to achieve the required therapeutic effect.[12, 13] In an interesting case report, a 33-yr-old woman experienced the acute onset (less than 30 min) of colicky abdominal pain, euphoria and dizziness following codeine 60 mg after a tooth extraction.[30] The same symptoms recurred following a second dose of 30 mg. She was later phenotyped and found to be an ultra-rapid EM. Rapid and extensive formation of morphine by *O*-demethylation of codeine was the suggested cause of these symptoms.

It has been suggested that a dose of codeine 1 mg kg^{-1} i.m. or orally in neonates and children is associated with a low risk of respiratory depression, although with repeated dosing this advantage may be lost.[94] In fact, there are few data on the non-analgesic effects of codeine in children. Respiratory and pupillary effects in comparison with other opioids have not been specifically investigated.

Post-operative vomiting after adenotonsillectomy in children has been found to be significantly less after codeine in comparison with morphine for 'equipotent' doses in a recent study.[102] Absence of or reduction in unpleasant or potentially dangerous side effects for equal analgesia in comparison with other opioids would be an important advantage for codeine. Unfortunately, the evidence for this is scant.

Conclusion

As the major proportion of the analgesic effect of codeine appears to be because of its metabolism to morphine, a large inter-individual variation in efficacy is to be expected with at least 9% of the UK population having little or no benefit. In effect, codeine administration may be regarded as a complicated and unreliable way of giving a low dose of morphine. As long ago as 1964, Lasagna noted that 'codeine possessed most of the disadvantages of morphine' and that 'its use could be avoided by using a dose of morphine less than 10 mg!'[66] Altered pharmacokinetic effects, particularly in the post-operative period, may also reduce its efficacy.

In early life, the immaturity of infant metabolic processes is also likely to reduce the efficacy of codeine. Furthermore, there is evidence that adverse effects may occur in the absence of analgesia in poor metabolizers of the drug. Genetic polymorphism may be an important factor responsible for the low efficacy of the drug in population studies and the high NNT in systematic reviews. It is interesting to note that during drug development those compounds subject to selective metabolism by polymorphic enzymes are often discarded in the early stages.[57] If codeine had been discovered today it is possible that it would not have made it as far as the pharmacy shelves.

The development of efficient and inexpensive methods of genotyping for enzyme polymorphisms, transport proteins and drug receptors may enable genetic information to be used in the future to tailor drug therapy for each individual.[57] However, until this type of screening is widely available, there is no way to accurately predict whether an individual patient will obtain a significant analgesic effect from a dose of codeine.

Overall there has been little clinical research into the use of codeine in children. From that which has been done it appears that the popularity of codeine in this patient group is not supported by convincing data of its efficacy or suitability, despite its apparently good safety record. The available evidence implies that codeine may in fact be particularly unsuitable for use in the younger child given the difficulties in pain reporting and assessment in this group and the unpredictable effects of the drug. In comparison with other opioids there is little evidence to support the commonly held view of a reduced incidence of serious side effects in the presence of equivalent analgesia. Further investigation in paediatric populations is required if its continued use is to be justified.

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BJA

SHORT COMMUNICATIONS

Predicted effect compartment concentration of thiopental at loss of eyelash reflex

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We derived the predicted effect compartment concentration of thiopental, at loss of the eyelash reflex, following three different injection regimens. Sixty patients were given thiopental for induction of anaesthesia. Twenty patients received multiple small boluses, 20 patients received a single bolus and 20 patients received an infusion. Computer simulation was then used to derive the effect compartment concentration. The median concentration was not significantly different between the three groups. EC_{50}, derived after combining all three groups was 11.3 μg ml^{-1}. The EC_{05}–EC_{95} range was 6.9–18.3 μg ml^{-1}, suggesting wide inter-individual variation.

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The concentration at the effect compartment has a hysteresis-free relationship with the pharmacological effect. The effect compartment can be viewed as another compartment receiving and returning drug to the central compartment, but is so small it has no influence on drug pharmacokinetics. As the effect compartment concentration cannot be measured directly, determination of its concentration requires simulation of the concentration–time profile using pharmacokinetic models.

It is usually assumed that a drug obeys a single set of pharmacokinetic parameters, regardless of whether it has being given by a bolus injection or by infusion. The aim of this study is to determine the predicted effect compartment concentration of thiopental, at loss of the eyelash reflex, when given using three different injection regimens. Knowledge of this concentration will allow the planning of dosage and infusion regimens to achieve a specific pharmacodynamic end-point while minimizing the risk of over dosage.

Methods and results

The study was approved by the local clinical research ethics committee. Sixty patients, American Society of Anesthesiologists physical class I or II, scheduled for elective surgical operations gave informed consent for the study. Patients with a history of cardiovascular disease were excluded from the study. No premedication was given. On arrival in the operating theatre, an intravenous cannula was inserted into a forearm vein for infusion of drugs and fluid.

The method of induction of anaesthesia differed according to which group the patient was allocated to by randomization.

Group 1: Intermittent bolus doses of thiopental; 50 mg boluses were given every 15 s until loss of the eyelash reflex was demonstrated.

Group 2: Single bolus dose of thiopental; 4 mg kg^{-1} was injected over 10 s.

Group 3: Continuous infusion of thiopental at 100 mg min^{-1}.

The eyelash reflex was tested every 2.5 s, and the time at which the reflex was lost was recorded. After induction of anaesthesia was successfully achieved, anaesthesia was maintained using a standard technique.

Effect compartment concentrations were predicted using the model reported by Stanski and Maitre.[1] Serum thiopental concentrations were first calculated using standard mathematical equations which were taken from reference 2 (Hull CJ. *Pharmacokinetics for Anaesthesia.* Oxford: Butterworth–Heinemann, 1991) (see Appendix). These equations are incorporated into an Excel spreadsheet

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Table 1 Patient data (mean (SD)), predicted effect compartment and serum concentrations (median (range)). Median effect compartment concentrations were not significantly different between groups. Predicted median serum concentrations were significantly different (P<0.05)

	Group 1 **Multiple boluses**	**Group 2** **Single bolus**	**Group 3** **Infusion**
n	20	20	20
Age (yr)	44.4 (25–64)	41.2 (20–62)	41.5 (23–66)
Weight (kg)	58.5 (43–77)	58.1 (46–74)	62.8 (40–80)
Gender (M/F)	11/9	9/11	9/11
Effect compartment concentration (μg ml^{-1})	10.3 (8.0–16.7)	10.6 (7.4–15.0)	13.2 (6.3–17.8)
Serum concentration (μg ml^{-1})	30.5 (23.8–39.8)	38.6 (34.0–43.7)	23.2 (15.7–30.6)

(V 5.0, Microsoft, Seattle, WA).[2] Effect compartment concentrations were then calculated using Euler's numerical solution.[3]

A sigmoid E_{max} model was then fitted to the concentration – effect data using the equation below:

$$\text{Probability of response} = \frac{C^s}{\text{EC}_{50}{}^s + C^s}$$

where C is the predicted effect compartment thiopental concentration, EC_{50} is the predicted effect compartment concentration at which 50% of the patients had loss of the eyelash reflex, and s is a dimensionless parameter characterizing the slope of the curve of the concentration–effect relationship. The curve was fitted by unweighted least-squares non-linear regression analysis using the program Microsoft Excel. The concentrations at which 95% and 5% of patients were non-responsive (EC_{95} and EC_{05} respectively) were also calculated.

Differences between median concentrations were tested using the Kruskall–Wallis test. A value of P<0.05 was considered significant.

The mean age and weight were similar between groups (Table 1). The median effect compartment concentration, at loss of the eyelash reflex, was not significantly different between groups (Table 1). In contrast, there was a significant difference in the median serum concentration (P<0.05). EC_{50}, derived after combining data from all three groups was 11.3 μg ml^{-1}, and s was 6.03. The EC_{05}–EC_{95} range was 6.9–18.3 μg ml^{-1}.

Comment

The median effect compartment concentration reported in this study is similar to those reported by previous investigators using loss of verbal response or loss of voluntary motor power as the end-point.[4 5] The median effect compartment concentration we derived is also similar to that obtained by computer simulation for jugular venous concentration at awakening from anaesthesia.[6] The jugular venous concentration reflects the brain concentration, and like the effect compartment concentration should be hysteresis-free. This would explain why the concentration and loss of consciousness and awakening are similar.

The median concentration for Group 3 (infusion) appears to be higher than that for Group 1 or 2, although this did not reach statistical significance. One reason for this could be the difficulty in accurately defining the point at which loss of the eyelash reflex occurred in the infusion group. In Groups 1 and 2, the effect compartment concentration at induction of anaesthesia was increasing rapidly because of the high serum–effect compartment concentration difference. In Group 3, the increase in effect compartment concentration was much slower, leading to a more gradual onset of effect. This made the onset of anaesthesia less distinct and could have led to a delay in the recording of the end-point.

In our study, the predicted effect compartment concentration at the pharmacodynamic end-point did not correlate with the age or weight of the patient. This could be because the pharmacokinetic-pharmacodynamic model incorporated both age and weight as covariates. This is an advantage as it avoids over dosage in elderly and thin patients.

Most manual dosing regimens and target controlled infusion systems rely on a series of bolus injections and infusion rates to achieve a desired plasma or effect compartment concentration. Optimal use of such infusion systems requires some form of real time estimation of drug concentration. Differences in the disposition of drugs cause the actual concentration achieved after a specific infusion regimen to differ from one patient to another. Knowing the measured concentration will allow an accurate correlation with effect. However, technology for such measurements is unlikely to be available in the near future. Real time prediction of the drug concentration offers a reasonable alternative at the present time.

Pharmacodynamic effect is assumed to be proportional to the concentration of the drug in the region of the receptors. Ideal infusion systems should be able to predict this concentration reliably despite the dosing history. The effect compartment concentration may not be the true concentration around the receptor sites, but this does not matter so long as it can be correlated with effect.

Target controlled infusion devices currently in use incorporate algorithms to predict drug concentrations. Results from our study suggest that concentrations predicted in such a fashion can be correlated to effect. While thiopental is not used for maintenance of anaesthesia, target controlled infusions of thiopental can still be used for induction. It is likely that other intravenous hypnotics will behave in a similar fashion, although this will need to be investigated further.

In conclusion, we found the predicted effect compartment concentration of thiopental at loss of the eyelash reflex to be independent of the injection regimen.

Appendix

Calculation of the predicted serum and effect compartment concentrations

To calculate the hybrid rate constants α, β, δ
Let:

$p = k_{31} + k_{21} + k_{12} + k_{13} + k_{10}$
$q = k_{21}k_{31} + k_{12}k_{31} + k_{13}k_{21} + k_{10}k_{31} + k_{10}k_{21}$
$r = k_{21}k_{31}k_{10}$
$a = (3q - p^2)/3$
$b = (2p^3 - 9pq + 27r)/27$
$\theta = \arccos\,[-(b/2) / \sqrt{-(a^3/27)}]$
$x_1 = 2\sqrt{-(a/3)}\cos\,[\theta / 3]$
$x_2 = 2\sqrt{-(a/3)}\cos\,[(\theta / 3) + 120]$
$x_3 = 2\sqrt{-(a/3)}\cos\,[(\theta / 3) + 240]$
$\alpha = (p/3) - x_2$
$\beta = (p/3) - x_3$
$\delta = (p/3) - x_1$

To calculate the instantaneous change in central compartment concentration with a bolus dose

$C^{\phi}_1 = C^{\phi}_1 + (X_d / V_1)$

To calculate change in central and peripheral compartment concentrations during an infusion and/or after a bolus dose

$F_1 = (k'_{01} / V_1) + C^{\phi}_1(k_{21} + k_{31}) + C^{\phi}_2k_{12} + C^{\phi}_3k_{13}$
$G_1 = (k'_{01} / V_1)(k_{21} + k_{31}) + C^{\phi}_1k_{21}k_{31} + C^{\phi}_2k_{12}k_{31} + C^{\phi}_3k_{13}k_{21}$
$H_1 = (k'_{01} / V_1)k_{21}k_{31}$
$J_1 = C^{\phi}_1$
$F_2 = C^{\phi}_1k_{21} + C^{\phi}_2(k_{12} + k_{13} + k_{31} + k_{10})$
$G_2 = (k'_{01} / V_1)k_{21} + C^{\phi}_1k_{21}k_{31} + C^{\phi}_2k_{31}(k_{12} + k_{10}) + C^{\phi}_3k_{13}k_{21}$
$H_2 = (k'_{01} / V_1)k_{21}k_{31}$
$J_2 = C^{\phi}_2$
$F_3 = C^{\phi}_1k_{31} + C^{\phi}_3(k_{12} + k_{13} + k_{21} + k_{10})$
$G_3 = (k'_{01} / V_1)k_{31} + C^{\phi}_1k_{21}k_{31} + C^{\phi}_2k_{31}k_{12} + C^{\phi}_3k_{21}(k_{13} + k_{10})$
$H_3 = (k'_{01} / V_1)k_{21}k_{31}$
$J_3 = C^{\phi}_3$
$A_i = [\alpha(J_i\alpha - F_i) + G_i - (H_i / \alpha)] / [(\beta - \alpha)(\delta - \alpha)]$
$B_i = [\beta(J_i\beta - F_i) + G_i - (H_i / \beta)] / [(\alpha - \beta)(\delta - \beta)]$
$D_i = [\delta(J_i\delta - F_i) + G_i - (H_i / \delta)] / [(\alpha - \delta)(\beta - \delta)]$
$E = k'_{01} / (V_1k_{10})$

Finally,

$C_i = A_ie^{-\alpha t} + B_ie^{-\beta t} + D_ie^{-\delta t} + E$

where C_1, C_2 and C_3 are the central, shallow peripheral and deep peripheral concentrations respectively.

To calculate the change in effect compartment concentration using Euler's numerical solution

The volume of the effect site (V_4) was arbitrarily defined as $V_1 / 10000$

$k_{41} = k_{eo}$
$k_{14} = k_{eo} / 10000$

To calculate the change in effect compartment concentration at each time interval:

$\Delta A_4 = [\,k_{14}A_1 - k_{41}A_4\,].\ \Delta t$

where A_1 and A_4 are the mass of drug in the central and effect compartments respectively, and Δt is the time interval. The time interval used in the simulation was 2.5 s. Therefore at any time, t:

$A_4\,(t) = A_4\,(t\text{–}2.5) + \Delta A_4$
$C_4\,(t) = A_4\,(t) / V_4$
$A_1\,(t) = C_1\,(t) \times V_1$

where C_1 and C_4 are the concentrations in the central compartment and effect compartments respectively.

Table 2 Pharmacokinetic model

Central volume (ml kg^{-1})	79
Transfer rate constants (min^{-1})	
k_{10}	0.0389
k_{12}	0.48 if age <35
	0.48–(0.00288×(age–35)) if age >35
k_{13}	0.107
k_{21}	0.0787
k_{31}	0.00389
$T_{\frac{1}{2}k_{eo}}$ (min)	1.17

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Effects of hypoxia and isoflurane on liver blood flow: the role of adenosine

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We investigated the role of endogenous adenosine in mediating the effects of hypoxia and isoflurane on portal tributary blood flow (PTBF) and hepatic arterial blood flow (HABF) in rats. Liver blood flows were determined using radiolabelled microspheres. Hypoxia resulting from the exposure of rats to an atmosphere containing 15% oxygen for 30 min decreased PTBF (23%) ($P<0.05$) and cardiac index (15%) ($P<0.05$), and increased HABF (78%) ($P<0.05$). Isoflurane (1.4 vol%) increased HABF in both normoxic and hypoxic conditions but did not affect PTBF. The adenosine receptor antagonist 8-phenyltheophylline attenuated the hypoxia-induced increase in HABF but did not affect that resulting from the administration of isoflurane. In conclusion, in contrast to the increase in HABF induced by hypoxia, that induced by isoflurane appears to be independent of endogenous adenosine.

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It has been suggested that changes in portal tributary blood flow (PTBF) lead to reciprocal changes in hepatic arterial blood flow (HABF) thereby maintaining total liver blood flow.[1] This response, termed the 'hepatic arterial buffer response,' is mediated in part through the action of locally produced adenosine.[1 2] Published studies[3] have reported that isoflurane increases HABF, an effect that has been attributed to preservation of the hepatic arterial buffer response. However, there are no direct data to substantiate this view.

We have previously reported that hypoxia decreases PTBF and increases HABF,[4] a pattern of change that is consistent with the buffer response. In the present study, we investigated the effects of hypoxia, isoflurane and their combination on blood flows to the liver, and we examined the role of endogenous adenosine in the hypoxia- and isoflurane-induced changes in liver blood flows using the adenosine receptor antagonist 8-phenyltheophylline.

Methods and results

With institutional approval, 60 fasting male Sprague-Dawley rats (Charles River Breeding Laboratories, Quebec, Canada) weighing 260–320 g were anaesthetized with isoflurane. Polyethylene catheters were inserted into: (1) the left femoral artery for arterial pressure monitoring and reference sample withdrawal, (2) the right internal jugular vein for fluid or drug infusion, and (3) the left ventricle via the right carotid artery for injection of radiolabelled microspheres, as we have described previously.[4–6] The rats recovered for 2 h and resumed normal behaviour. They were assigned at random to awake or isoflurane (1.0 MAC, 1.4 vol%) groups and breathed either 30 or 15% oxygen. Hypoxic rats were pre-treated with either 8-phenyltheophylline infused at a rate of 0.2 mg kg^{-1} min^{-1} for 60 min or an equal volume of normal saline. 8-Phenyltheophylline was mixed in normal saline at a pH of 11.6 as described previously.[6] Animals breathed spontaneously in individual Plexiglas containers through which the inspired mixture was delivered (5 litre min^{-1}). The inspired concentration of isoflurane was monitored continuously using a calibrated infrared gas analyser (Sensormedics LB2, Anaheim, CA, USA). Normothermia was maintained using heating lamps.

After at least 30 min with each inspired mixture, cardiac index and liver blood flows were determined using 15±0.1 μm diameter ^{57}Co-labelled microspheres (New England Medical, Boston, MA, USA) as we have reported previously.[4–6] Briefly, approximately 50 000 microspheres

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Table 1 Systemic haemodynamics and liver blood flows and vascular resistances in awake and isoflurane-anaesthetized rats. Values are mean)(SD). *$P<0.05$ compared with awake 30% oxygen, †$P<0.05$ compared with isoflurane 30% oxygen, ‡$P<0.05$ compared with corresponding value in awake rats, §$P<0.05$ compared with awake 15% oxygen+normal saline

	Awake			**Isoflurane (1 MAC)**		
	30% O$_2$ (*n*=11)	**15% Oxygen+ saline (*n*=11)**	**15% Oxygen +8-PT (*n*=8)**	**30% Oxygen (*n*=11)**	**15% Oxygen+ saline (*n*=11)**	**15% Oxygen +8-PT (*n*=8)**
Mean arterial pressure (mm Hg)	104 (13)	85 (10)*	98 (15)	83 (13)*	91 (10)	87 (14)
Cardiac index (ml min^{-1} kg^{-1})	256 (20)	217 (23)*	223 (17)*	239 (20)	215 (27)	208 (48)
Portal tributary blood flow (ml min^{-1} kg^{-1})	44.4 (8.4)	34.0 (7.0)*	31.9 (9.6)*	40.6 (10.1)	36.5 (6.8)	29.2 (6.8)†
Hepatic arterial blood flow (ml min^{-1} kg^{-1})	11.1 (2.3)	19.8 (6.8)*	13.6 (4.6)	17.6 (9.1)*	20.6 (5.1)	20.7 (4.6)‡
Pre-portal vascular resistance (mm Hg ml^{-1} min^{-1})	2.4 (0.5)	2.5 (0.5)	3.0 (0.7)	2.1 (0.6)	2.5 (0.4)	2.9 (0.7)
Hepatic arterial vascular resistance (mm Hg ml^{-1} min^{-1})	9.3 (2.0)	4.4 (1.9)*	7.2 (2.3)*§	4.9 (1.5)*	4.4 (1.6)	4.2 (1.5)‡

were infused into the left ventricle over 20 s. A reference sample was drawn from the femoral artery at a rate of 0.6 ml min^{-1} starting 10 s before the microsphere infusion. The rats were killed and the liver, kidneys, spleen, stomach, small intestine, and large intestine were removed for determination of radioactivty (Nuclear Chicago, model 1185, Chicago, IL, USA). The mixing of microspheres in the circulation was considered adequate if there was less than a 15% difference in the left and right renal blood flows. Cardiac index, liver blood flows and vascular resistances were calculated using standard formulae.[4] Arterial blood gases were determined in separate groups of rats given one of the four inspired gas mixtures.

Data are expressed as mean (SD). Two-way ANOVA and the Student Newman–Keuls test were used to compare systemic haemodynamics and liver blood flows. Student's *t*-test was used to compare arterial pH and blood gases. $P<0.05$ was considered statistically significant.

In awake rats, hypoxia decreased PTBF by 23% ($P<0.05$) but did not change pre-portal vascular resistance (Table 1). The reduction in PTBF was offset by a 78% increase in HABF ($P<0.05$) (Table 1). Isoflurane did not significantly affect the portal circulation but did increase HABF by 59% ($P<0.05$) and decreased hepatic arterial vascular resistance by 47% ($P<0.05$). Pre-treatment with 8-phenyltheophylline attenuated the hypoxia-induced increase in HABF in awake rats but did not affect that induced by isoflurane (Table 1). Hypoxia resulted in a small degree of alkalosis in both the awake (pH 7.49 (0.04) in hypoxic *vs* 7.38 (0.02) in normoxic rats, $P<0.05$) and isoflurane (pH 7.48 (0.02) *vs* 7.35 (0.03), $P<0.05$) groups, a decrease in arterial carbon dioxide tension that was significant only in the isoflurane group (4.6 (0.2) *vs* 5.8 (0.5) kPa, $P<0.05$), and a significant decrease in arterial oxygen tension in both the awake (7.5 (0.5) *vs* 20.8 (0.5) kPa, $P<0.05$) and isoflurane (8.6 (0.2) *vs* 20.4 (0.7) kPa, $P<0.05$) groups.

Comment

We found that pre-treatment with the non-specific adenosine receptor antagonist 8-phenyltheophylline attenuated the increase in HABF induced by hypoxia in awake rats, but did not affect that resulting from the administration of isoflurane. These data suggest that the hypoxia-induced increase in HABF is mediated in part by endogenous adenosine, whereas that produced by isoflurane is independent of adenosine and is presumably secondary to a direct vasodilator effect of isoflurane upon the hepatic artery. At the dose used in the present study, we have shown that 8-phenyltheophylline does not modify basal mean arterial pressure or PTBF.[6] We have also shown that this dose of 8-phenyltheophylline completely antagonized the increase in splanchnic blood flow induced by administration of adenosine in the rat.[6] These studies support our present findings that a hepatic arterial buffer response to reduced PTBF occurs in the rat and that 8-phenyltheophylline can attenuate this response.

Radiolabelled microspheres were used to determine liver blood flows in the present study. This technique has been used extensively in studies of the splanchnic circulation and yields accurate estimates of cardiac output and liver blood flows.[7,8] The number of microspheres used in the present study causes minimal haemodynamic disturbance while being sufficient to measure liver blood flows accurately.[7] The validity of our absolute blood flow values is substantiated by previous work from this laboratory[4–6] and others.[7]

In the present study, rats breathed spontaneously in order to permit valid comparisons among the treatments and avoid the need for interventions such as basal anaesthesia and positive pressure ventilation that can reduce liver blood flow. Accordingly, the hypoxic and isoflurane-anaesthetized rats were mildly hypocapnic and hypercapnic, respectively. These changes in carbon dioxide tension, however, were small relative to those previously shown to influence the splanchnic circulation.[9,10]

In conclusion, in contrast to the hypoxia-induced increase in HABF that induced by isoflurane appears to be independent of endogenous adenosine. The present results suggest that isoflurane enhances HABF in both normoxic and hypoxic conditions and may thereby confer a protective effect upon the liver.

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Heterogeneous distribution of cardioplegic solution in pigs

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Septal dyskinesia in the left ventricle is detected frequently in many patients after open-heart surgery. The present study was designed to determine whether the antegrade delivery of cardioplegic solution to the regional wall categorized in echocardiography is homogeneous, and whether the distribution to the septal wall differs from that to the lateral wall in the absence of coronary artery disease. To assess these hypotheses quantitatively, radioactive microspheres were mixed into the cardioplegic solution and infused by an antegrade method in eight normal pigs. The cardioplegic distribution to the septal wall was significantly less than to the lateral wall close to the base of the left ventricle ($P<0.05$). Therefore, antegrade perfusion of cardioplegic solution was non-uniformly distributed to the regional and transmural wall of normal pig hearts. Absence of functional correlation was a limitation of this study. However, these findings suggest that inadequate protection of the ventricular septum by antegrade cardioplegia might be an explanation for the abnormalities of septal wall motion after open-heart surgery.

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Newly developed septal wall motion abnormalities are detected frequently after valve and coronary bypass surgery. The role of pericardiotomy with secondary loss of pericardial restraint, perioperative ischaemia and intrapericardial collections have been suggested as the causes of this abnormality.[1] However, non-homogeneous delivery of cardioplegic solution may result in postischaemic myocardial injury. Aldea *et al.*[2] found that flow to discrete myocardial regions was significantly non-homogeneous for both antegrade and retrograde cardioplegia.

We propose two experimental hypotheses that are based on previous work: (i) the antegrade delivery of cardioplegic solution to the regional wall categorized in echocardiography may be heterogeneous in the absence of coronary artery

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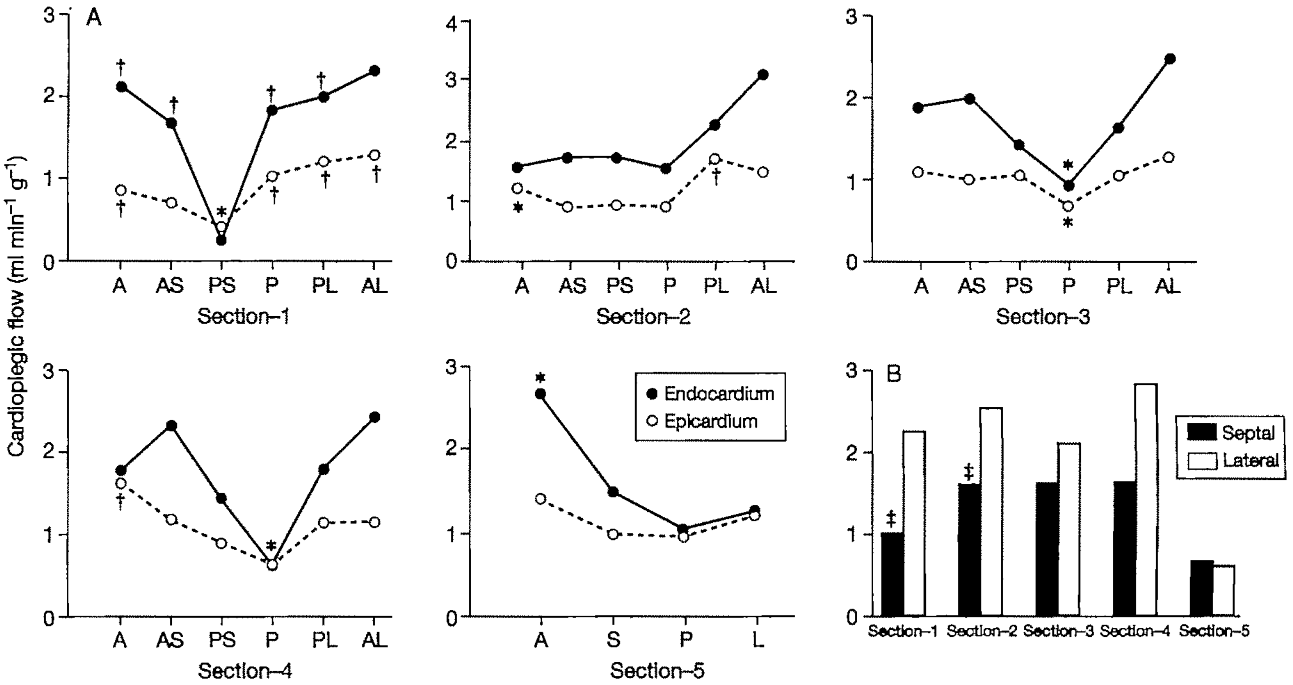

Fig 1 Cardioplegic flow in the regional wall (A) and septal versus lateral wall distribution (B) of the left ventricle. (A) Subendocardial data are shown as solid circles and subepicardial data as open circles. AS=anteroseptal; PS=posteroseptal; A=anterior; P=posterior; AL=anterolateral; PL=posterolateral; S=septal; L=lateral segment. $^{*}P<0.05$ compared with median flow of the AS segment; $^{\dagger}P<0.05$ compared with median flow of the PS segment. (B) Cardioplegic distribution to the septal wall is shown as solid bars and cardioplegic distribution to the lateral wall as open bars. $^{\ddagger}P<0.05$ compared with lateral wall in each cross-section. Data are medians. Section 1 shows basal LV; Section 5 shows apical LV; Sections 2, 3 and 4 show mid-LV.

disease; and (ii) the distribution of cardioplegic solution to the septal wall may differ from that to the lateral wall.

Methods and results

Eight Yorkshire pigs (weighing 25.3 (1.6) kg; range 20–30 kg) were studied after approval had been obtained from the Animal Care Committee of Ajou University Institute for Medical Sciences. All animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* (NIH Publication 85–23, revised 1985; National Institutes of Health, USA). After premedication with a mixture of ketamine hydrochloride 10 mg kg^{-1}, midazolam 0.1 mg kg^{-1} and atropine sulphate 0.05 mg kg^{-1} i.m., anaesthesia was induced with ketamine 1–2 mg kg^{-1} i.v. and tracheostomy was performed. Anaesthesia was maintained with a mixture of 100% oxygen and 0.5–1.0% halothane. For muscle relaxation, pancuronium bromide 0.2–0.3 mg kg^{-1} was administered i.v. The animals were ventilated with a Harvard respirator (Harvard Apparatus, Natick, MA, USA).

Median sternotomy was performed and the pericardium opened. About 3 min after heparinization (10 000 U), a drainage cannula was inserted into the right atrial appendage and connected to 1 litre bags. An aortic root cannula was also inserted for delivery of cardioplegia. The cardioplegic solution (Cardio Sol®; Choongwae, Kyungkee, Seoul, Korea) contained potassium 16 mEq litre^{-1}, and extra potassium was added to yield 20 mEq per 500 ml. The solution was cooled (4°C) in an ice-bath, and about 200 000 microspheres of diameter 15 µm and labelled with chromium 51 (NEN-TRAC® Microspheres, NEM-032A; New England Nuclear, Du Pont Diagnostic Imaging Division, North Billerica, MA, USA) were injected into the bag containing the cardioplegic solution. The volume of cardioplegic solution was 20 ml kg^{-1} body weight.

Vascular isolation of the heart was accomplished by sequentially clamping the azygos vein, inferior and superior venae cavae, main pulmonary artery and ascending aorta. Cardioplegic solution was infused into the aorta with a roller pump (COBE®; COBE Laboratories, Lakewood, CO, USA) at a rate sufficient to maintain a perfusion pressure (measured at the aortic root with a transducer) of approximately 90–100 mm Hg until asystole was obtained on the ECG. The volume of fluid in the drainage bag was measured and three samples were obtained to assay the concentration of radioactivity. The heart was excised and placed in formalin solution for 3–5 days to facilitate sectioning. The left ventricle (LV) was divided into five cross-rings from base to apex.[3] The four rings from the basal and mid-wall were divided into six full-thickness sections and the apical ring was divided into four sections. To correlate the regional wall motion abnormalities by echocardiography with the distribution of cardioplegic solution, the LV was divided into 16 segments as recommended by the American Society of Echocardiography.[4] The free wall of the right ventricle (RV) was divided into six basal and six apical segments.[3] Each section of both ventricles was divided into subendocardial and subepicardial halves. Each tissue sample was weighed and placed in counting tubes and analysed for γ-radioactivity (Cobra II; Packard Instrument, Downers Grove, IL, USA).

The flow rate of cardioplegic solution in each sample (Q_m) was calculated using the equation $Q_m = (C_m/C_t) \times Q_t$, where C_m is the radioactivity of the myocardial sample, C_t is the total radioactivity in all of the heart tissue and Q_t is the total cardioplegic flow rate (total volume of cardioplegic solution/time required for infusion). Flow rate may underestimate total flow if a significant fraction of microspheres are shunted across the circulation. Therefore, cardioplegic flow was corrected by dividing cardioplegic flow by the extraction fraction.[3] To obtain the extraction fraction, shunt fraction was calculated by dividing the concentration of radioactivity (counts min^{-1} ml^{-1}) in the RV effluent by the concentration of radioactivity (counts min^{-1} ml^{-1}) in the cardioplegic solution.

Statistical analysis was performed by repeated measures analysis of variance and the Wilcoxon signed ranks test. A probability of $P<0.05$ was considered significant.

We studied eight animals. The median LV and RV flow was 1.30 (range 0.73–1.85) and 1.16 (0.14–1.78) ml min^{-1} g^{-1} and the relative distribution of cardioplegia between RV and LV was 0.97 (0.18–1.03).

Distribution of cardioplegic solution to discrete myocardial regions of the LV is shown in Fig. 1A. The distribution of cardioplegic solution around each LV cross-section was uneven. Heterogeneous distribution was prominent in basal cross-section (section 1). The median cardioplegic flow of total basal RV and total apical RV was 1.22 (0.20–1.40) and 1.09 (0.08–2.22) ml min^{-1} g^{-1}, and there was no significant difference between them. Cardioplegic distribution in the free wall of the RV was relatively uniform (no statistical difference between each of the six samples within basal and apical RV of both groups).

Median septal versus lateral wall distribution in the LV was 1.55 (0.86 to 1.76) versus 2.45 (1.29 to 3.99) ml min^{-1} g^{-1} (not statistically significant). However, in LV cross-sections the cardioplegic distribution to the lateral wall was significantly greater than that of the septal wall in sections 1 and 2 (Fig. 1B).

Distribution of cardioplegia within both ventricles was significantly greater in the subendocardium than in the subepicardium. Median subendocardial to subepicardial ratio (endo/epi ratio) of the LV was 1.97 (1.66–2.55) in the septal wall, 1.52 (1.11–2.23) in the anterior wall, 2.10 (0.99–3.35) in the lateral wall and 1.53 (0.96–2.04) in the posterior wall, and the endo/epi ratio of the septal wall was significantly higher than that of the posterior wall. There was no significant difference between basal (1.58) and apical (1.31) endo/epi ratios of the RV.

Comment

We confirmed that there was a significantly higher distribution to the lateral wall compared with the septal wall closer to the basal LV in normal pig hearts. Although the reason is not clear, we postulate that there might be some collateral circulation to the distal septal wall through small endocardial anastomoses between the right and left coronary arteries.[5]

Many experiments dealing with cardioplegia have supported the idea that non-homogeneous delivery of cardioplegic solution might result in postischaemic myocardial injury. Aldea *et al.*[6] reported that, even in hearts with normal coronary anatomy, some regions of the myocardium may have limited delivery of cardioplegic solution and thus inadequate protection. However, Stirling *et al.*[3] reported that antegrade cardioplegic distribution around each LV cross-section was relatively uniform compared with retrograde cardioplegic distribution in the canine model.

Distribution to the RV has been shown to be two-thirds of that to the LV, and LV subepicardial distribution was approximately one-half of subendocardial flow in canine hearts.[7] Our results revealed that median RV distribution was about 97% of that to the LV. The fact that a greater RV/LV ratio is reported here can be explained as a species difference. For example, the left circumflex coronary artery and left anterior descending artery each supply about 40% of the myocardium, whereas the right coronary artery supplies about 15% in the dog. In pigs, the right coronary and left anterior descending arteries are about equal and the left circumflex plays a relatively minor role, as in man.[8] We also obtained results for the endo/epi ratio similar to those reported previously.[7] More abundunt subendocardial perfusion may be related to the greater capillary density and decreased capillary resistance compared with the epicardial surface. Interestingly, the distribution to the posterior, especially subendocardial wall was less than that to the anterior septal wall in mid-papillary and mid-lower cross-sections (sections 3 and 4) (Fig. 1A). This finding corresponds to a significantly lower endo/epi ratio of the posterior wall compared with the septal wall. Therefore, these results suggest that posterior LV walls could be more vulnerable to inadequate myocardial protection.

There are two limitations of our investigation. First, extrapolation to the human should be considered cautiously, because there are species differences in coronary anatomy. The animal model most commonly used for coronary circulation studies has been the dog. Dogs seem to have a collateral system that is extensive and highly recruitable: they usually have three or four relatively large subepicardial collateral vessel anastomoses. There seems to be little doubt that the pig coronary vascular system is closer to that of man.[9] Secondly, the limitations of this study include the lack of demonstration of a functional outcome of cardioplegic distribution. Assessment of regional myocardial performance in regions that did and did not receive adequate cardioplegia would help to support the assumption that cardioplegic delivery is essential for providing myocardial protection.[10] However, we could not investigate the relationship between cardioplegic distribution and functional recovery because intraoperative echocardiography was not available in our laboratory.

In conclusion, antegrade perfusion of cardioplegic solution was non-uniformly distributed to the regional and transmural walls of normal pig hearts. Although further functional studies are needed, inadequate protection of the ventricular septum by antegrade cardioplegia might be one of the explanations for postoperative septal wall motion abnormalities after open-heart surgery.

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BJA

CASE REPORTS

Liver transplantation for massive hepatic haemangiomatosis causing restrictive lung disease

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A 34-yr-old man with hepatic haemangiomatosis presented for orthotopic liver transplantation. His massively distended abdomen caused thoracic compression and severe restrictive lung disease. Respiratory failure was the principal indication for transplantation. Increased airway pressures, pulmonary hypertension, systemic hypotension caused by aorto-caval compression, and blood loss, complicated the intra-operative anaesthetic management. Weaning from mechanical ventilation was impaired by acute and chronic metabolic alkalosis, and diaphragmatic laxity.

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Cavernous haemangiomas are the most common benign tumour of the liver and may occur in association with systemic haemangiomatosis.[1 2] Giant haemangiomas (>4 cm in diameter) are rare, but may cause abdominal discomfort and coagulopathy (Kasabach-Merritt syndrome[3]) or can rupture.[4] Orthotopic liver transplantation for haemangiomatosis is unusual, and less than 15 patients have been described.[4–14] We report a patient with massive hepatic haemangiomatosis causing restrictive lung disease who had a liver transplant. To our knowledge, this is the first transplant primarily for the treatment of restrictive lung disease.

Report of patient

A 34-yr-old man presented for liver transplantation because of massive liver haemangiomatosis that affected his respiratory function. He had presented elsewhere 16 yr before with abdominal pain, and laparotomy and biopsy revealed multiple cavernous haemangiomas in the liver. He also had evidence of a systemic haemangiomatosis syndrome, with haemangiomas in the mandible, eye socket, and hands. Attempted hepatic resection via a thoracoabdominal approach was abandoned because of excess bleeding. He underwent hepatic artery embolization and cholecystectomy. Two years later, repeat hepatic artery embolization was carried out in an attempt to limit the growth of the tumour but this was unsuccessful and he was referred to our institution. Further surgical intervention was not felt to be possible. He was treated with alpha-interferon, which has been reported to be of use in infantile hepatic haemangioendotheliomatosis,[15] but without success and the disease progressed.

Over the years, as his liver tumour grew, the patient's condition gradually worsened. Two months before transplantation, he became weak and lethargic, with dyspnoea on minimal exertion, persistent abdominal discomfort, and peripheral oedema. His abdomen was massively distended, and he had to remain upright at all times because of shortness of breath. Examination showed jugular venous distention and markedly diminished lung air-entry.

The chest radiograph (Fig. 1A) showed bilateral raised hemidiaphragms with small lung fields. Computerized axial tomography (CT) (Fig. 2A) of the thorax showed a compressed pulmonary vascular bed, especially in the lung bases, and abdominal CT (Fig. 2B) showed massive hepatomegaly. Transthoracic echocardiography was normal except for a mildly dilated right atrium, moderately dilated right ventricle, and an elevated pulmonary artery systolic pressure estimated at 56 mm Hg. There was no evidence of right to left shunt.

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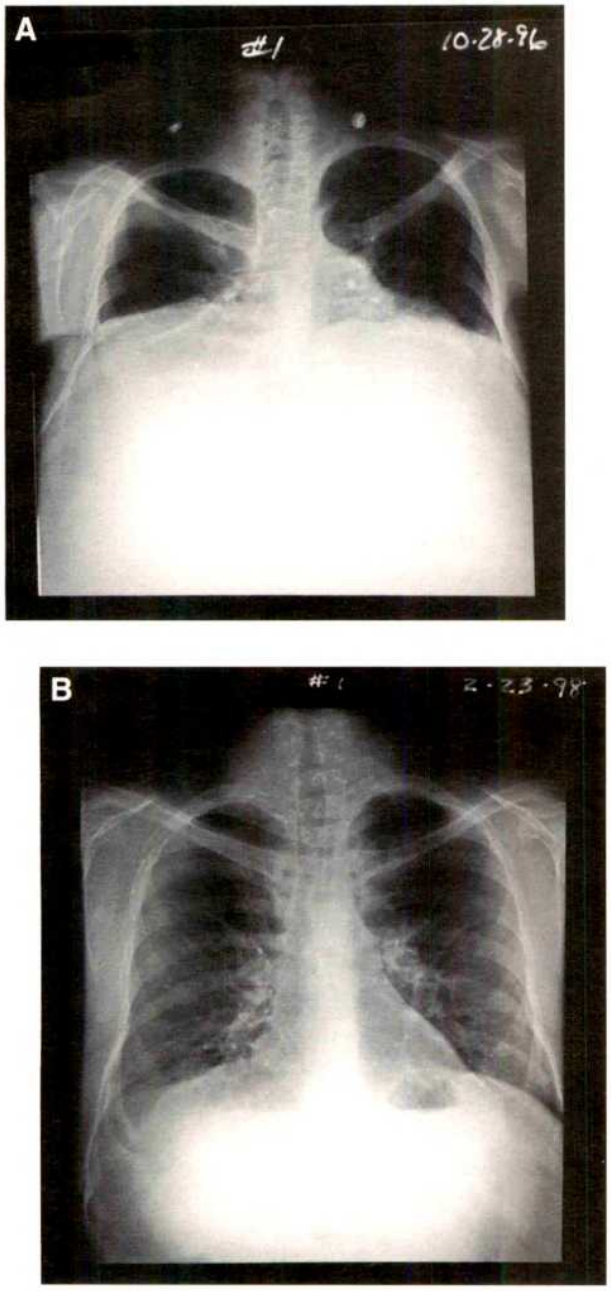

Fig 1 Chest radiographs before and after surgery showing compression of the patient's lungs by liver haemangiomatosis, and the improvement after its removal.

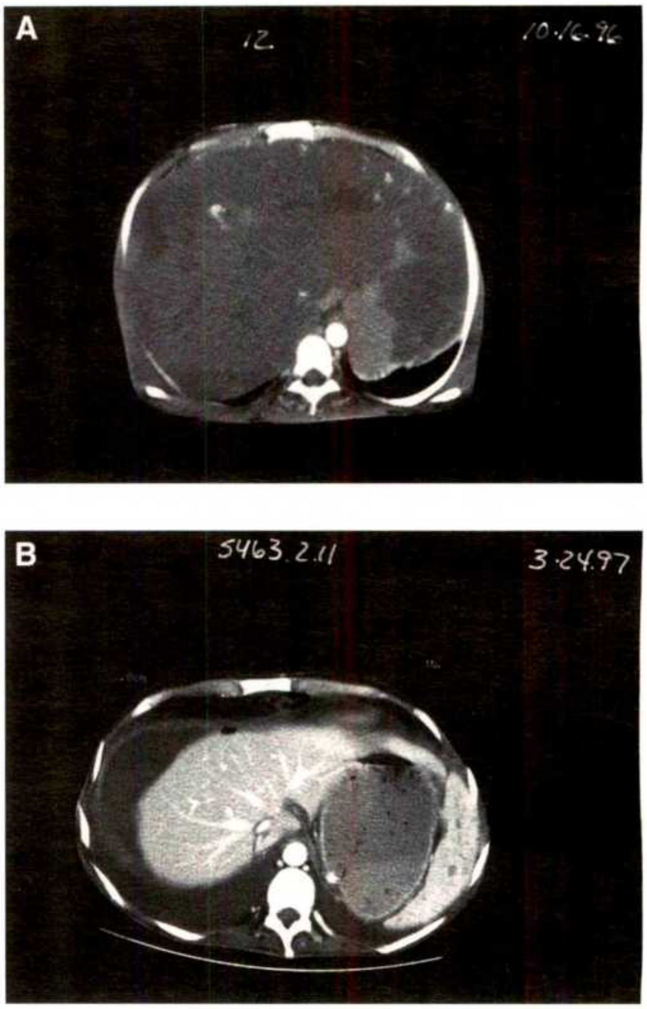

Fig 2 Contrast-enhanced computerized axial tomography scans of the abdomen before and after surgery. There is enlargement of the liver to almost completely fill the abdominal cavity. The image after surgery includes a fluid collection and is of a different anatomical level, but the new liver clearly takes up less space in the abdomen.

Arterial blood gas analysis showed hypoxaemia (Pa_{O_2} 7.6 kPa, Sp_{O_2} 86% on room air), hypercarbia (Pa_{CO_2} 8.2 kPa), and complete metabolic compensation for the respiratory acidosis (pH 7.4, HCO_3^- 37 mEq litre^{-1}, base excess +11). Pulmonary function tests (Table 1) were notable for a severe restrictive process with forced expiratory volume in 1 s (FEV_1) 1.26 litre (29% of predicted) and a proportional decrease in forced vital capacity (FVC) at 1.73 litre (32% of predicted). His diffusing capacity of the lung for carbon monoxide (DLCO) was 2.87 (41% of predicted). Supplemental, low-flow (1–2 litre min^{-1}) oxygen was required. Liver function tests were abnormal: Aspartate transminase (AST) at 123 unit litre^{-1} total bilirubin 41 mmol litre^{-1} and alkaline phosphatase 1213 unit litre^{-1}, and International normalized ratio (INR) 1.4. Haematological tests showed a decompensated intravascular coagulation, thrombocytopaenia, and fibrinolysis (fibrin split products >40 mg ml^{-1}, ref. <10; fibrinogen 108 mg dl^{-1}, ref. 175–350; activated partial thromboplastin time 36 s, ref. 21–33; platelet count 104×10^9 litre^{-1}, ref. 150–450). On the day of surgery blood gas deteriorated: Pa_{O_2} 7.2 kPa, Pa_{CO_2} 12.4 kPa, pH 7.33, HCO_3^- 49 mEq litre^{-1}, base excess +21.

The patient was brought to the operating room, standard monitors applied and a left radial arterial catheter placed. While in the sitting position, the patient was sedated with midazolam 1 mg and scopolamine 0.8 mg i.v. and the abdomen was prepared for surgery. Oropharyngeal and transtracheal local anaesthesia was administered and endotracheal intubation was carried out with fibreoptic

Table 1 Pulmonary function tests performed 1 month before transplantation and 1 month after transplant, demonstrating the improvement in the restrictive pulmonary physiology. The FVC after surgery may not be complete

Test	Pre-transplant	1 Month post-transplant
FVC	1.73 litre	2.06 litre
FEV_1	1.26 litre	1.93 litre
FEV_1/FVC	72.6%	94%
FEF_{25-75}	0.9	2.6
FEF_{MAX}	3.8	5.0
MVV	41 litre	71 litre

guidance with the patient in a semi-sitting position. General anaesthesia was induced with sevoflurane in oxygen. Despite being lowered slowly into the supine position, systolic blood pressure decreased from 130 to 70 mm Hg, but responded to i.v. fluid and 20 μg adrenaline. Large-bore i.v. cannulae were placed and an oximetric pulmonary artery catheter inserted. Initial pulmonary artery systolic and diastolic pressures were 44 and 28 mm Hg, respectively. Anaesthesia was maintained using a combination of isoflurane in air/oxygen with fentanyl (approximately 20 $\mu g\ kg^{-1}$ delivered in divided doses). Pancuronium was used for muscle relaxation.

The surgical dissection was complicated by adhesions from the previous cholecystectomy. The liver was densely adherent to the abdominal wall in the areas near the previous incisions. Near the site of the previous thoracoabdominal incision, the distal portions of the ribs were embedded within the hepatic parenchyma and haemangioma. The abdominal wall was excised bilaterally in a wedge-shaped fashion between the umbilical area and the flank. While removing the liver from its attachment to the abdominal wall, significant bleeding was encountered, and thus the portal vein was ligated, starting the anhepatic phase. (The hepatic artery had been ligated earlier in an effort to decrease potential arterial bleeding.) The liver was removed, leading to improvement in ventilation (tidal volume 300 ml and rate 16 min^{-1} with peak inspiratory pressures of 30 cm H_2O, to tidal volumes of 500 ml without an increase in pressures). Pulmonary artery pressures decreased to 29/15 mm Hg. After removal of the liver, there was redundancy of the previously stretched diaphragm. The anhepatic phase lasted 142 min and reperfusion was tolerated without significant incident. Total transfusion requirements during surgery were to 40 units banked red blood cells, 79 units 'Cell Saver' (Hemonetics, Braintree, MA, USA), 50 units of fresh frozen plasma, 30 units of platelets, and 60 units of cryoprecipitate. A rapid transfusion device (Hemonetics) was used to give fluids and blood products. The resected liver weighed 19 kg and measured 63×45×51 cm. Large parts of redundant abdominal wall skin, subcutaneous tissue and muscle were resected before abdominal closure. The bulk of the tumour was confirmed histologically to be cavernous haemangioma.

The patient was transferred to the intensive care unit (ICU). Continued intra-abdominal bleeding caused haemodynamic instability. Haemostasis was secured after repeat laparotomy, with subsequent haemodynamic stability.

On the second post-operative day the patient was alert and co-operative and a trial of weaning from intermittent mandatory ventilation was attempted. While on continuous positive airway pressure (CPAP) of 5 cm H_2O and pressure support of 10 cm H_2O, his CO_2 increased to greater than 13 kPa. Bedside pulmonary mechanics were obtained and these showed maximal inspiratory and expiratory pressures of −18 and +2 cm H_2O, respectively. Over 8 days in the ICU, the patients' maximal inspiratory and expiratory pressures improved to −20 and +40 cm H_2O, respectively. His spontaneous vital capacity improved from 500 to 1450 ml during the same period of time. The patient was weaned to spontaneous ventilation with 5 cm H_2O CPAP and pressure support of 10 cm H_2O. He mobilized in the ICU while attached to a portable ventilator and improved sufficiently to allow extubation of his trachea 8 days post-operatively. Post-extubation blood gases (FI_{O_2} 0.21) were Pa_{O_2} 9.2 kPa, Pa_{CO_2} 6.6 kPa, pH 7.39 and serum bicarbonate concentration 30 mEq $litre^{-1}$. He left hospital 2 weeks after transplantation.

Pulmonary function tests 1 month after surgery, showed marked improvement in his restrictive lung pattern (Table 1) with FEV_1 increased to 1.93 litre (45% predicted). Subsequently, lung function and overall quality of life have continued to improve. One year later, his chest x-ray (Fig. 1) showed improvement in lung volumes and a rounded contour to the diaphragm. Arterial blood gases (room air) showed a P_{O_2} of 12.1 kPa, P_{CO_2} 6.1 kPa, HCO_3^- 28 kPa and pH 7.4. His transplanted liver continues to function satisfactorily.

Discussion

Haemangiomas are the only common vascular tumour of the liver and are the most common benign liver tumour. The incidence is reported as being between 0.4 and 20% in autopsy series.[1] Most haemangiomas remain small and asymptomatic and are identified at post-mortem or incidentally as a result of investigation for other conditions. Haemangiomas are mostly solitary, but 10% have multiple locations and may occur as part of a systemic haemangiomatosis syndrome. Those with a diameter of greater than 4 cm are defined as giant haemangiomas.

Giant haemangiomas may be managed expectantly especially if surgical resection is thought to be technically difficult or if the patient has minimal or no symptoms.[12 16] When patients become symptomatic the options for therapy include hepatic artery embolization[17] and surgical resection. There have also been reports of the use of corticosteroids and radiotherapy in the management of the lesions.[18] Orthotopic liver transplantation (OLT) has been used for giant liver haemangiomas, the principal indications being pain, functional debility, and risk of rupture. There are less than 15 such patients reported in the literature. In our patient, the principal reason for transplantation was the severe restrictive lung disease.

The anaesthetic management of OLT is challenging and in this patient the difficulties were compounded by several unusual features. First, despite the fact that his airway looked favourable, there was concern that, haemodynamically, because of aortocaval compression, the patient would not tolerate a rapid sequence induction. In addition, the patient could not lie flat because of dyspnoea. Awake fibreoptic endotracheal intubation was performed, and inhalation induction of anaesthesia using sevoflurane followed. In spite of a slow change to the supine position the patient did become hypotensive, but this was responsive to fluid and vasopressor administration. Left lateral tilt could also have been used to decrease aorto-caval compression, in a fashion analogous to the use of left uterine displacement in pregnancy.

Second, his pulmonary hypertension (PA systolic pressure 56 mm Hg on pre-operative testing) was a concern. It was felt that, in the current patient, this was almost entirely because of mechanical factors caused by his massive liver lesion and would be reversible post-transplant. Pulmonary artery pressures did decrease (mean pulmonary artery pressure 33–20 mm Hg) after the patient's liver was removed.

Finally, for a number of reasons, the patient was likely to breathe poorly after surgery. His already elevated bicarbonate concentration (49 mEq litre^{-1}, ref. 22–28) and the massive blood transfusion requirements containing citrate, caused severe metabolic alkalosis and central hypoventilation. The stretching of the diaphragm by the large liver conferred some mechanical advantage pre-operatively but once the liver was removed the diaphragm became lax.[19] In addition, his malnourished state (a result of pre-operative early satiety from gastric compression and consequent decreased caloric intake) and compressed lungs from tumour mass impaired respiratory function. Each of these factors could prolong mechanical ventilation, but extubation of the trachea was possible 1 week after the transplantation.

In summary, we present a patient with massive hepatic haemangiomatosis, which caused a restrictive-type of respiratory failure. Transplantation was successful in spite of concerns of elevated airway pressures, pulmonary hypertension, severe metabolic alkalosis, inherent surgical difficulties and possible aorto-caval compression. Transplantation improved the patient's respiratory status and overall quality of life.

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Undiagnosed cardiomyopathy in a neonate: significance of low oxygen saturation during anaesthesia

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A case study is described of a 7-day-old full term baby with bilateral congenital cataracts who underwent surgical removal of both cataracts 2 days apart. Problems with oxygen saturation during and after the first anaesthetic prompted further investigation that revealed a non-obstructive hypertrophic cardiomyopathy. The significance and possible causes of low oxygen saturation in a previously healthy neonate during anaesthesia are discussed. The likely diagnosis of Sengers syndrome, and the evaluation of asymptomatic babies with cardiac pathology are discussed.

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A healthy term baby with no dysmorphic features was found to have absent red reflexes (bright light is prevented from reflecting off the vascular retina by an opacity) at an otherwise normal routine post-natal examination. Dense bilateral congenital cataracts were confirmed and urgent planned surgery arranged to remove the cataracts on separate occasions, 2 days apart. The baby weighed 2600 g on day 7 and had been fasted from milk formula for 6 h. Anaesthesia was induced through an *in situ* i.v. cannula with thiopental 10 mg after atropine 20 µg. Muscle relaxation was achieved using atracurium 1.5 mg before tracheal intubation with a size 3.0 uncuffed tracheal tube. Anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen 50–60%, and the baby ventilated to an E'_{CO_2} of 4.8–5 kPa.

Monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, gas monitoring (FI_{O_2}, E'_{CO_2}, and ET-volatile), pre-cordial stethoscope, axillary temperature, and ventilation pressure and failure alarms.

Oxygen saturation (Sa_{O_2}) remained between 85 and 92% despite meticulous confirmation of tracheal tube placement. Manual chest inflation, re-intubation, and an FI_{O_2} up to 90% did not alter the Sa_{O_2}. The chest remained clear on auscultation. An insignificant difference in Sa_{O_2} of only 2% was noted between pre-ductal (right arm) and post-ductal (leg) sites. End-tidal sevoflurane concentrations of 1.7–2.0% maintained a systolic arterial pressure of between 65 and 75 mm Hg. I.v. 4% dextrose/saline was infused at a rate of 4 ml kg^{-1} h^{-1} during the 90 min of anaesthesia in addition to 40 ml of calculated fluid deficit. Normothermia was maintained.

The only other abnormality noted was elevation of ST segments on standard lead I. Emergence and extubation after reversal of residual neuromuscular block with neostigmine 100 µg and atropine 20 µg were uncomplicated. The trachea was free of secretions. The baby was returned to the neonatal unit with a Sa_{O_2} of 94%, breathing oxygen 30% and in no apparent respiratory distress. As no satisfactory explanation could be offered for the oxygenation difficulties experienced perioperatively, a neonatologist was consulted about the possibility of undetected congenital cardiac or pulmonary disease.

On return to the neonatal unit, examination revealed a pink and well-perfused baby with normal pulses and heart sounds. Chest x-ray confirmed clear lung fields but showed an enlarged heart. ECG revealed ST segment elevation in AVL, I, II, V4 and V6, with T wave inversion in lead III.

Overnight the baby needed oxygen 30% to maintain a Sa_{O_2} of 95%, but feeding was commenced without difficulty early the next morning, and oxygen therapy was gradually weaned. An echocardiogram on the first post-operative day revealed a markedly thickened left ventricular free wall and interventricular septum, without outlet obstruction, consistent with non-obstructive hypertrophic cardiomyopathy (HCM). No other structural abnormalities were noted. The arterial duct was closed but the foramen ovale was small and

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Table 1 Disorders associated with neonatal hypertrophic cardiomyopathy (HCM)

Noonan syndrome	Dysmorphic features (short stature, webbed neck, hypertelorism), cardiac malformations
Beckwith-Wiedemann syndrome	Macroglossia, exomphalos, visceromegaly, hypoglycaemia
Pompe disease	Glycogen storage disease type II, hepatosplenomegaly, poor muscle tone, high voltage ECG complexes
Fatty acid oxidation defects	Abnormalities in mitochondrial β-oxidation and transport of long chain fatty acids and carnitine
Mitochondrial abnormalities (e.g. Sengers syndrome)	Abnormal mitochondrial DNA resulting in cardiac or brain dysfunction
Trisomy 21	(Down syndrome)
Mucopolysaccharidoses	Infiltrative disorders with dysmorphic features and visceromegaly

patent. Blood glucose was normal, and investigations for metabolic and chromosomal causes (Table 1) proved negative.

Two days later the second cataract was removed. Thiopental was omitted and anaesthesia was induced with sevoflurane in oxygen. Management and conduct of anaesthesia were otherwise as before, although an inspired oxygen concentration of 50–60% resulted in a Sao_2 between 90 and 93% on this occasion. There was no post-operative oxygen dependence after the second operation.

Discussion

Risk analysis in more than 22 000 paediatric anaesthetics shows that neonates have the highest incidence of intra-operative events, and respiratory causes (airway obstruction, laryngospasm, bronchospasm, apnoea) are the most frequent.[1] The trachea of a term neonate is only 4 cm in length and the smallest movement of the head during surgery can displace the tracheal tube. The use of a precordial stethoscope positioned in the left axilla facilitates continuous intra-operative confirmation of air entry.

An Sa_{O_2} that remains persistently low despite exclusion of respiratory causes, and especially when unresponsive to increased oxygen administration, must raise concerns about the presence of an intra-cardiac or cardiopulmonary shunt. Congenital cyanotic heart disease is usually recognizable. However, this baby was well oxygenated pre-operatively and had displayed no signs suggestive of cardiac problems.

Transition from the fetal to neonatal circulation is not a single event; it is regarded as a process consisting of several phases.[2] It is important to recognize that there are times during this transition when the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) may fluctuate to the extent that pulmonary blood flow will be significantly affected. The normal decline in PVR to adult values takes place within the first 2 weeks of life.[3]

This baby was clinically well before the induction of anaesthesia despite having significant HCM. The low intra-operative Sa_{O_2} might have occurred as a result of myocardial dysfunction, accompanied by a degree of right-to-left intra-cardiac shunting.

Thiopental is known to be a dose-dependant myocardial depressant and capable of lowering SVR.[4] Oxygenation during and after the second anaesthetic, in which thiopental was omitted, was better. Although volatile anaesthetics generally depress the myocardium, sevoflurane has been shown to maintain contractility and cardiac index in infants.[5] An anaesthetic technique using high dose fentanyl will produce less myocardial depression, although it may affect SVR.[6] This technique also necessitates post-operative ventilation, and was not felt to be indicated in this baby.

Right-to-left shunting commonly occurs in neonates with persistent pulmonary hypertension (PPHN). Shunting from right to left across a patent arterial duct will result in a difference between pre-ductal and post-ductal Sa_{O_2}. This was not observed in our patient. Right-to-left shunting at the level of a patent foramen ovale (PFO) can result in a global reduction in oxygenation, however, as seen in this baby.

Right-to-left inter-atrial shunting occurs in newborns because the mitral valve opens before the tricuspid valve, resulting in the left atrial pressure (LAP) decreasing before the right atrial pressure.[7] PPHN or right ventricular dysfunction secondary to HCM may have induced a right-to-left inter-atrial shunt through the PFO in this baby. Another factor to consider is the role of anaesthesia in lowering SVR and LAP.

Common causes of HCM have been excluded in this baby. The co-existence of congenital cataracts and HCM raises the possibility that this baby suffers from Sengers syndrome, characterized by cataract, cardiomyopathy, and mitochondrial cytopathy.[8] Definitive diagnosis may be possible and requires a fresh muscle biopsy that can be analysed in only a few specialized units. Neonatal death secondary to severe cardiomyopathy has been reported in which clinical evidence of episodic tachypnoea and cyanosis had been noted within days of birth.[9] HCM associated with mitochondrial cytopathy has been diagnosed in several adults in whom the only early clues to the diagnosis had been the presence of bilateral cataracts at birth and poor exercise tolerance throughout life.[10]

Neonates with HCM present in a variety of ways ranging from asymptomatic to severely ill.[11] Presentation by desaturation during anaesthesia is unusual. Typically, asymptomatic neonates are evaluated for heart disease after either the detection of a heart murmur during routine neonatal examination, a family history of congenital heart disease (CHD), or a history of pregnancy-related problems such as maternal diabetes mellitus and hydrops fetalis.

Although most babies in the UK undergo routine neonatal examination within the first day of life, it is unreliable for detecting CHD. Routine neonatal examination detects CHD in only 45% of patients, and severe disease is no more likely to be detected.[12] In one study murmurs were heard on routine examination in 0.6% of babies, 50% of whom had CHD.[13] CHD commonly exhibits no signs or symptoms in the first few days of life, and the diagnosis in some cases is only made at post-mortem.[14]

The significance of an unexplained, low Sa_{O_2} observed during anaesthesia in our patient is quite evident, and raises important considerations. Anaesthetists must be aware of the physiological implications of the transitional circulation during the first 2 weeks of life. There is no reliable clinical means of detecting cardiac pathology in apparently healthy neonates. A low threshold for suspecting cardiac malformations in asymptomatic neonates with associated abnormalities is warranted. Comprehensive assessment and baseline investigations are recommended before surgery in such cases, including chest x-ray, ECG and echocardiography.

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Multiple acyl-CoA dehydrogenase deficiency: a rare cause of acidosis with an increased anion gap

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Metabolic acidosis is encountered frequently in intensive care and common causes include lactic acidosis, ketoacidosis, or renal failure. We describe a patient presenting to intensive care with a rare cause of metabolic acidosis associated with an increased anion gap: multiple acyl-CoA dehydrogenase deficiency. The pathophysiology of this condition is discussed along with potential treatment options.

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Metabolic acidosis is measured using the pH scale. The use of this logarithmic relationship means that small changes in pH represent large changes in hydrogen ion concentration and consequently a significant insult to the substantial buffering capacity of the body. These changes should be investigated and treated aggressively. We present a patient with metabolic acidosis and increased anion gap. The pathophysiology of this condition and potential treatment options are discussed.

Case history

A 31-yr-old lady presented with a 1-day history of diarrhoea, vomiting, and confusion that had been preceded by a week of dysuria and fever for which she had not sought treatment. On the morning of admission she complained of worsening abdominal symptoms and became progressively agitated and confused. She had a previous medical history of parasuicide (sedative overdose) requiring admission 1 month previously, and her partner expressed concern that this may have recurred. She drank alcohol excessively and had recently returned from a Mediterranean holiday. On initial examination she was afebrile, tachycardic (rate 120 beat min^{-1}) normotensive and had cool peripheries. Examination of her chest was normal but she had marked suprapubic tenderness. The results of her initial haematology and biochemistry investigations were essentially normal apart from small increases in urea (9.5 mmol litre^{-1}), amylase (156 unit litre^{-1}) and alanine transaminase (ALT) (86 unit litre^{-1}). Her blood glucose on admission was 5.4 mmol litre^{-1}.

She deteriorated markedly in the hours after admission and became unrousable, tachypnoeic, hypotensive, and oliguric. Arterial blood analysis revealed a profound metabolic acidosis (pH 7.0, P_{O_2} 24 kPa, P_{CO_2} 4.2 kPa, base excess –18 mmol litre^{-1}) and her blood sugar had now decreased to an unrecordable concentration. Fifty mililitres of Dextrose 50% was administered with little effect on her conscious level and she was admitted to intensive care.

On admission to intensive care she developed severe circulatory failure (heart rate 146 beat min^{-1}, arterial pressure 70/30 mm Hg) and her breathing became progressively laboured. She was given volume resuscitation with colloid but respiratory failure required tracheal intubation and mechanical lung ventilation with a high minute volume. Oesophageal Doppler monitoring (after initial volume resuscitation) confirmed a high cardiac output and high-corrected flow times consistent with a low peripheral vascular resistance. Despite further volume resuscitation her arterial pressure continued to decrease and she did not respond to epinephrine and norepinephrine infusions. Review of her acid–base status revealed a persistent metabolic acidosis (base excess now –20 μmol litre^{-1}), an anion gap of 40 mmol litre^{-1} and an arterial lactate of 0.9 mmol litre^{-1}. Severe cardiovascular instability with persistent acidosis prompted administration of bicarbonate 50 mM as a resuscitative measure, a bicarbonate infusion and continuous haemodiafiltration. After partial correction of her acidosis her cardiovascular system responded to dobutamine 5 μg kg min^{-1} and norepinephrine 1 μg kg min^{-1}.

The diagnosis at this point was still unclear so we investigated the possibility of poisoning. Blood obtained before to resuscitation revealed a plasma ammonia of 52 μmol litre^{-1} and measured plasma osmolality of 318 mOsm kg^{-1} (calculated osmolarity of 298 mOsm litre^{-1}). Urine was sent for drug analysis on admission to intensive care and urgent microscopy did not reveal any oxalate crystals (metabolite of ethylene glycol). Ketones were absent in this urine sample. The presence of an increased osmolar gap raised the possibility of methanol toxicity and as a result an i.v. infusion of ethanol was commenced (10 g h^{-1} by i.v. infusion, aiming for a plasma concentration of 1–2 g litre^{-1}). This was discontinued the following day when urinalysis, at our hospital, confirmed that ethanol, methanol, and ethylene glycol were not present. Specialist analysis of the urine was also requested from our regional centre the next morning and this revealed the presence of large quantities of dicarboxylic acids, small amounts of abnormal acylglycines, normal lactate, and mildly elevated ketones. This picture was consistent with the rare metabolic disorder multiple acyl-CoA dehydrogenase deficiency (MADD) and this diagnosis was reinforced later by results from ensuing outpatient investigation. Abnormal organic acid production was limited by a 10% Dextrose infusion (aiming to keep blood glucose between 5 and 10 mmol litre^{-1}), carnitine (100 mg kg day^{-1}) and riboflavin (300 mg day^{-1}) supplements. The rationale for this treatment is discussed below. At this stage the metabolic acidosis had started to resolve with supportive treatment and her inotropic support was decreased accordingly. The metabolic acidosis fully resolved after 3 days and she was weaned from cardiovascular, respiratory, and renal support over the next 2 weeks.

Discussion

Metabolic acidosis in patients requiring intensive care is common, but is normally a result of the production of lactic acid, ketoacids, or renal failure. The most striking feature of this case was the severe persisting acidosis without apparent cause. On initial presentation to intensive care the combination of hypoglycaemia with minimal ketosis could have alerted us to the possibility of an in-born error of lipid metabolism; however, the first presentation of such a disorder in an adult is extremely rare.[1]

When determining the cause of a metabolic acidosis it is useful to calculate the anion gap. A high anion gap (as seen in this case) is most often accounted for by uraemia, ketoacidosis (diabetic, alcoholic), and lactic acidosis. Exogenous acids may also increase the anion gap and in the absence of an alternative, as in this case, poisoning with salicylate, methanol, or ethylene glycol should be con-

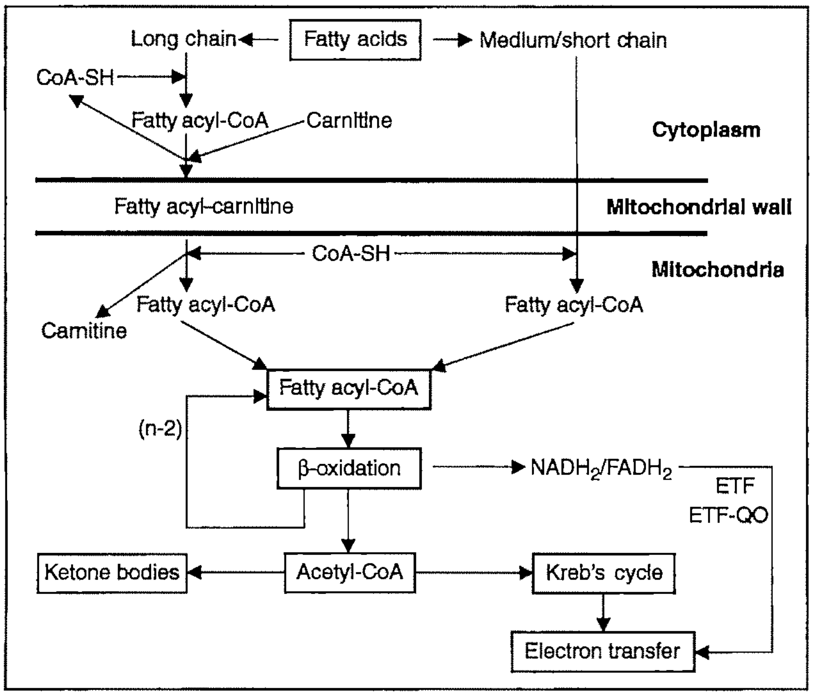


Fig 1 The pathways involved in normal β-oxidation of fatty acids. In order to metabolize fatty acids it is first necessary to transport them into the mitochondria. Once inside the mitochondria then β-oxidation can follow. MC-DCA, medium chain dicarboxylic acid; SC-DCA, short chain dicarboxylic acid; CoA-SH, coenzyme A; ETF, electron transfer flavoprotein; ETF-QO, electron transfer flavoprotein ubiquinone, (coenzyme Q) oxidoreductase.

sidered.[2] Salicylate poisoning was excluded but the diagnosis of alcohol poisoning is more difficult. Specialist laboratories are able to measure plasma/urinary alcohol but this is often not available immediately. The diagnosis of alcohol poisoning may be aided by estimation of the osmolar gap ([measured plasma osmolality]–[calculated plasma osmolarity]).[3]

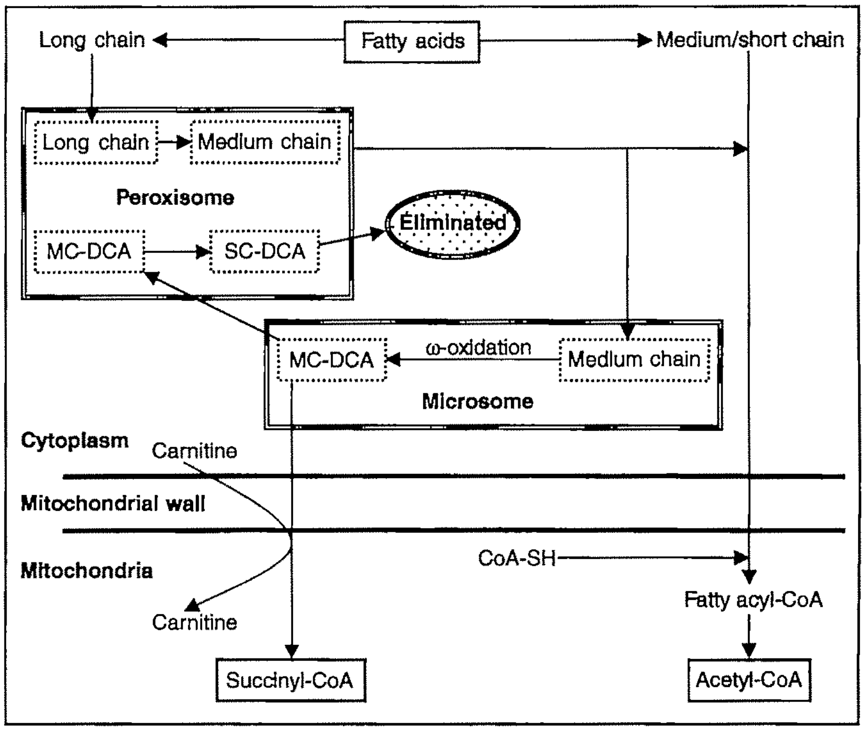
To determine the osmolar gap the laboratory must measure plasma osmolality. This can be measured by two techniques: the vapour pressure technique and the depression of freezing point technique. When considering alcohol toxicity it is important to ensure that the measured osmolality is derived by depression of freezing point (the vapour pressure method will cause volatile alcohols to evaporate prematurely generating an inaccurate result).[4]

The osmolar gap is arbitrarily defined as raised when greater than 10 mOsm and in this case it was increased to 20 mOsm.[3] The use of the osmolar gap in alcohol poisoning is controversial for several reasons. A normal gap does not exclude toxicity (especially important with ethylene glycol toxicity where toxic concentrations of the poison exert minimal osmotic influence)[5] and a raised gap does not necessarily confirm the presence of alcohol. In the absence of an obvious cause for the acidosis and the presence of a raised osmolar gap we treated our patient for presumed methanol ingestion. Methanol is metabolized to formaldehyde (by alcohol dehydrogenase) and subsequently to formic acid (by aldehyde dehydrogenase). The symptoms and toxicity from methanol are related to the rapid production of the osmotically active aldehyde metabolite. Alcohol dehydrogenase metabolizes ethanol in preference to methanol and an infusion of ethanol will limit the production of formaldehyde and serve as a useful treatment for methanol poisoning. An ethanol infusion was commenced in this case until the laboratory was able to definitively exclude alcohol poisoning.

The correct diagnosis was conclusively reached when urine samples were analysed at a tertiary referral centre for the presence of abnormal organic acids. This was requested the day after admission to intensive care and the results were available the same day. The gas chromatography-mass spectrometry profile proved consistent with a defect in lipid metabolism, MADD. The pathophysiology of this condition is best explained by initial reference to how fatty acids are normally metabolized.

Normal fatty acid metabolism

Fatty acid metabolism provides a major source of energy for cardiac and skeletal muscle. Free fatty acids are bound to albumin in the plasma and diffuse across the cell membrane to enter the cytoplasm. The subsequent pathways involved in normal metabolism are shown in Fig. 1. Short (4–6 carbon atom) and medium (8–12 carbon atom) chain fatty acids are able to enter the mitochondria directly for metabolism but long chain fatty acids require a transport mechanism. The mechanism for translocating long chain fatty acids utilizes L-carnitine and an enzyme system. The



KEY	
MC-DCA	Medium chain dicarboxylic acid
SC-DCA	Short chain dicarboxylic acid
CoA-SH	Coenzyme A
ETF	Electron transfer flavoprotein
ETF-QO	Electron transfer flavoprotein ubiquinone (coenzyme Q) oxidoreductase

Fig 2 Alternative pathways available for handling fatty acids. When the pathways for β-oxidation are unavailable, cytoplasmic peroxisomes and microsomes are utilized for ω-oxidation of fatty acids. This produces short chain dicarboxylic acids that are eliminated in the urine.

fatty acid is transported as a fatty acyl-carnitine and when inside the mitochondria carnitine is released leaving fatty acyl-CoA. Metabolism is then possible using β-oxidation, a four enzyme loop, cycles repeatedly liberating acetyl-CoA, $FADH_2$, and NADH thus shortening the fatty acid by two carbon atoms each cycle.[6] The β-oxidation reactions are directly coupled to coenzyme Q of the electron transfer chain through electron transfer flavoprotein (ETF) and electron transfer flavoprotein–ubiquinone (co-enzyme Q) oxidoreductase (ETF-QO). These flavoproteins are also required by two similar mitochondrial enzymes isovaleryl-CoA and glutaryl-CoA dehydrogenase and defects in these flavoproteins will therefore affect oxidation of long, medium, and short chain fatty acids and the metabolism of the amino acids lysine and leucine. Alternative pathways for long chain fatty acid oxidation exist and these become heavily utilized when fatty acid metabolism is defective.

Alternative pathways for fatty acid metabolism (Fig. 2)

In the liver long chain fatty acids are able to enter cytoplasmic peroxisomes where they are enzymatically oxidized to medium chain acids. This reaction does not require carnitine and does not produce ATP. The medium chain acids have two fates as shown in Fig. 2: to enter the mitochondria for oxidation to acetyl-CoA or to transfer to cytoplasmic microsomes where the ω carbon atom is hydroxylated by cytochrome p450 mono-oxygenase and then oxidized to dicarboxylic acids. The dicarboxylic acids are then either transported to the mitochondria by carnitine for oxidation to succinyl-CoA or they are transported back to the peroxisome for oxidation to short chain dicarboxylic acids that are then excreted in the urine.[7]

The patient presented was found to have a gross dicarboxylic aciduria and was diagnosed as suffering from MADD. This condition is a rare in-born error of lipid metabolism (incidence unknown) that is transmitted as an autosomal recessive trait. In this condition one of the flavoproteins ETF or ETF-QO function incorrectly and as a result all the acyl dehydrogenase enzymes (short, medium, and long) involved in β-oxidation are unable to function effectively. (The metabolism of lysine and leucine is also affected.)[8]

MADD has several documented forms that vary according to the degree of enzyme deficiency. The severe variety normally presents in the neonatal period (glutaric aciduria type II) and is associated with an absence of ETF-QO. Acidosis is profound and hypoglycaemia, coma, and multiple-organ dysfunction normally result in a fatal outcome. A milder variety has been documented (ethylmalonic-adipic aciduria) which tends to present in later life and has a better outcome.[9]

In MADD, β-oxidation is defective so any condition that encourages increased fatty acid metabolism (starvation/ gastroenteritis) will cause alternative metabolic pathways of lipid metabolism to be utilized and ω-oxidation of fatty acids will ensue.[10] If the alternative enzyme system is overwhelmed then longer chain dicarboxylic acids will also appear. Acetyl-CoA production is impaired and gluconeogenesis is unable to maintain plasma glucose during the stress. This causes severe hypoglycaemic episodes that are typically associated with minimal ketone production. Unlike other acyl-CoA dehydrogenase deficiencies (medium chain being the most common with an incidence of 1:10–20 000)[9] MADD also produces a severe metabolic acidosis caused in part to the production of dicarboxylic acids but also caused by the defect in electron transport in the mitochondria and associated inability to produce water from hydrogen ions. The inability to utilize fatty acylcarnitine will cause an increase in plasma concentrations (detected by analysis of blood spots on Guthrie cards)[11] and a secondary deficiency of carnitine.[12] Carnitine is required to transport dicarboxylic acids from the microsome to the mitochondria and this secondary deficiency will encourage further short chain dicarboxylic acids to be produced. Carnitine treatment in this case was effective at eliminating isovaleryl carnitine but also encouraged production of longer chain carnitines that were excreted in urine inadequately.

The milder variant of MADD is also termed riboflavin responsive dicarboxylic aciduria.[7] The partial loss of enzyme activity seen in this condition can be minimized by supplementing riboflavin (the cofactor for ETF and ETF-QO). Riboflavin was given in the case presented but it was discontinued later because of limited efficacy. Many features of severe MADD were present in the case presented even though this condition rarely presents in adulthood. The milder variant tends to produce minimal acidosis, a different urinary organic acid profile and a better response to riboflavin. It is likely that this case represents a variant of severe MADD but we are unsure why this case should present at this late stage. It is possible that the combination of an inadequate diet over the week before admission (she had drunk significant amounts of alcohol and eaten poorly while abroad), gastroenteritis, and a urinary tract infection created such a demand on lipid metabolism that the acidosis was precipitated. Before this event her limited ability to metabolize lipids by β-oxidation and sufficient carbohydrate reserves prevented normal metabolic stresses causing an attack. After discharge she was advised to keep to a regular diet, avoid fasting, limit her alcohol intake, and was maintained on carnitine supplements.

When treating patients with a severe non-lactate acidosis on intensive care it is important to consider and exclude the common causes such as alcohol poisoning. However, if the diagnosis is still elusive then the importance of system support and basic intensive care principles cannot be overemphasized. The patient presented had started to respond with the supportive measures described to treat the acidosis before the diagnosis was confirmed. These measures allow time for more precise investigation and specific treatments to be implemented.

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Subarachnoid haemorrhage following spinal anaesthesia in an obstetric patient

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We describe an obstetric patient who presented for removal of a retained placenta. After insertion of the spinal anaesthetic, she developed a severe headache, and a subarachnoid haemorrhage was diagnosed. We discuss the differential diagnosis of the headache, the occurrence of intracranial haemorrhages after dural puncture and the future management of this patient.

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Severe headache in combination with pregnancy and dural puncture has a broad spectrum of differential diagnoses, including postdural puncture headache, pre-eclampsia, migraine, drug-induced headache and intracranial pathologies. The latter include haemorrhages, venous sinus thrombosis and postpartum cerebral angiopathy. Although rare, subarachnoid haemorrhage (SAH) was the second commonest cause of indirect maternal death in the most recent triennial report (1994–1996) on maternal deaths from the UK's Department of Health.[1] This diagnosis should be considered when assessing obstetric patients with atypical headaches after dural puncture.

Case report

A 29-yr-old, multiparous woman (gravida 4 para 3) presented for removal of a retained placenta. Her previous obstetric history consisted of three spontaneous vaginal deliveries, including one with a retained placenta that was removed uneventfully under spinal anaesthesia 4 years ago. Except for a history of smoking (25 cigarettes per day) and mild asthma, there was no notable medical history, and the patient was normotensive throughout this pregnancy. As there were signs of fetal distress, she required an assisted instrumental delivery. A healthy, normal-sized baby (Apgar score 7 at 1 min and 9 at 5 min) was delivered after 5 h 20 min of labour (second stage 15 min). Medication given during labour included ranitidine 150 mg orally, patient-controlled Entonox, and Syntometrine 1 mg i.m. on delivery of the baby.

One hour after delivery she was moved to theatre for removal of a retained placenta. The anaesthetic registrar performed a spinal anaesthetic with the patient in the right lateral position, at the level of the L3/4 interspace using a 24G Sprotte needle under standard aseptic conditions. At the first attempt, clear cerebrospinal fluid (CSF) was obtained, and this was followed by slow injection of 2.5 ml heavy bupivacaine. At 5 min a sensory block to T6 was achieved and the operation proceeded. Systolic blood pressure ranged between 130 and 90 mm Hg and the intraoperative heart rate was stable at 65–85 beats min^{-1}. Boluses of ephedrine were given as required in 3 mg increments to a total of 15 mg.

Five minutes into the operation, the patient complained of a sudden onset of severe, pounding, occipital headache radiating to the frontal region. Neurological examination revealed photophobia, no meningism, no additional motor or sensory deficits and a Glasgow coma score of 15. Systolic blood pressure recorded at the onset of the headache was 150 mm Hg, with a heart rate of 80 beats min^{-1}. No ECG changes were noted. Further medication given intraoperatively included Augmentin 1.2 g i.v. and an infusion of Syntocinon (30 IU in 500 ml of normal saline over 2 h). The placenta was removed manually and the patient was transferred back to the labour room for observation. She still complained of severe headache and felt nauseated with one episode of vomiting. There was no postural element to the headache. Cyclizine 50 mg i.v. and codeine phosphate 60 mg orally were given. One hour later the headache was still incapacitating. Investigations at this time included a normal coagulation screen (prothrombin time 11.1 s, control 13.2 and activated partial thromboplastin time 31.6 s, control 32.7) and full blood count (haemoglobin 12.3 g dl^{-1}, platelets 292 $\times\sim10^9$ litre^{-1}). The on-call medical team was consulted and a cranial computer tomogram performed, which showed a small amount of blood in the left sylvian

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fissure and the convexity sulci. The diagnosis of an SAH (grade 1 on the Hunt and Hess scale) was made and the patient was transferred to a neurosurgical unit on the same day. A four-vessel angiogram demonstrated tortuous vasculature on the left, but no apparent lesion. A repeat angiogram 6 weeks later was normal. The patient has made an uneventful recovery.

Discussion

Spontaneous SAH is a rare event, ruptured intracranial aneurysms being the main cause (51–80%), followed by hypertensive disease (10–15%) and arteriovenous malformations (AVM) (5–10%). Rarer causes include meningeal infection, tumours and blood dyscrasias.[2 3] In 5–10% of spontaneous SAHs, no causative lesion can be identified.[3 4] The incidence of spontaneous SAH is estimated to be increased five-fold to 2 in 100 000 deliveries compared with the non-pregnant population, but no reliable data exist.[5] Several studies confirm a higher risk of aneurysmal rupture during pregnancy, whereas the behaviour of an AVM in the pregnant patient is more controversial,[5–9] except for an increased risk of rebleeding of an AVM during pregnancy.[6 7] The risk of an SAH increases with gestational age, probably because of hormonal and haemodynamic changes of pregnancy. Although one would assume that labour itself poses a particular risk, only 2% of SAHs occur during labour.[5] Uterine contractions and the Valsalva manoeuvre performed during vaginal delivery cause a marked transient increase in blood pressure as well as in CSF pressure. This may balance the transluminal pressure across a fragile vessel wall.[7 10] According to a recent review,[5] there is consensus that an SAH in a pregnant patient should be treated according to the same neurosurgical principles valid for the non-pregnant patient.

In our patient, severe headache occurred suddenly a few minutes after insertion of a spinal anaesthetic and about 2 h after vaginal delivery. The differential diagnosis included early onset of a postdural puncture headache, caused by CSF loss and subsequent low CSF pressure. In our case, there was neither sufficient time for significant CSF loss through a 24G hole in the dura, nor any significant CSF loss during spinal needle insertion. The presentation of headache was atypical, with a sudden, severe onset and no postural element. Pre-eclampsia was considered, but there was no hypertension or proteinuria. Tension headache or migraine was unlikely because the onset of headache was too sudden and severe, with no history of similar headaches. The ephedrine given just before the onset of the headache may have caused a sudden change in blood pressure, resulting in headache. In our patient the headache lasted several hours, extending far beyond the normal period of drug action. After exclusion of the common causes of headache, intracranial pathology was considered and a computer tomogram performed, which revealed the SAH.

Very few reports describe intracranial haemorrhages after dural puncture and most of these are subdural haematomas.[11–16] A potentially continuing CSF leak leads to low CSF pressure with pulling on the dura and bridging veins, causing postdural puncture headache. If this headache is left untreated, the shearing forces can lead to venous tears and acute or chronic subdural haematoma. Typically, the patient presents with prolonged postdural puncture headache, which becomes treatment-resistant, with loss of the postural element, and neurological symptoms and signs develop. At this point the intracranial haemorrhage is usually diagnosed. Postdural puncture headache should be taken seriously and treated early to minimize the rare but potentially fatal complication of an intracranial haemorrhage.

On review of the literature, only three cases of intracerebral haemorrhage[17–19] and only one case of an SAH alone[20] have been reported after a dural puncture. In the latter, Boettiger and colleagues[20] describe a 60-yr-old man who developed an SAH after two consecutive subarachnoid blocks within 2 weeks. They postulate that low CSF pressure exacerbated by the second dural puncture can develop even without postdural puncture headache. The decrease in intracranial pressure could cause an increase in transmural pressure across the arterial wall, thus facilitating the rupture of a potential vascular malformation.

In our patient, there was insufficient time for a significant CSF leak to develop and, therefore, the pathophysiology of an intracranial haemorrhage, postulated by other authors, may not apply here. Just before the onset of the headache, i.v. ephedrine was given because the systolic blood pressure had dropped to 90 mm Hg. Although the maximum recorded value afterwards was only 150 mm Hg, the pressure was measured non-invasively every 3 min and might have briefly been higher. Relatively sudden swings in blood pressure could have facilitated the rupture of a potentially weakened vessel wall before autoregulation became effective. Aneurysms are known to rupture under conditions associated with sudden rises in blood pressure.[21]

Considering the sequence of the events, there is the possibility that the SAH occurred during or just after labour, although the patient did not complain about headache at that time, and became symptomatic as a result of increased bleeding around the time the spinal block was performed. Potential cardiovascular changes, as discussed earlier, may have contributed to this. On the other hand, the combination of labour, spinal anaesthetic and SAH might have been purely incidental, considering that many spontaneous SAHs occur without obvious trigger event. In one series of 500 patients, 34% of SAHs developed during non-strenuous activities and 12% during sleep.[22] Such a coincidence is, however extremely unlikely as the overall incidence of SAHs is so low.

The computer tomogram in our patient showed a small SAH. The four-vessel angiogram was negative on the same day and 6 weeks later. According to Latchaw and colleagues,[3] in 10% of SAHs found on CT scan no lesion can be identified on the angiogram. This usually implies a better prognosis, with a rebleeding rate of 4%.[4]

How should this patient be managed if she presents with another pregnancy? According to Dias and Sekhar,[9] maternal and fetal outcomes are similar in parturients with either untreated aneurysms or AVMs, regardless of whether a Caesarian section or a vaginal delivery is performed. Manoeuvres such as shortening the second stage, epidural analgesia and, if necessary, low forceps delivery might decrease the risk of recurrent bleeding during vaginal delivery.[9] If this patient requires anaesthetic intervention in the future, we will probably avoid spinal anaesthesia, although case numbers are too small to provide sufficient evidence favouring a general anaesthetic. If an epidural catheter is considered, it should be inserted by an experienced operator to minimize the risk of a dural tap, which could be disastrous. She should be assessed antenatally by a consultant obstetric anaesthetist to formulate a management plan for labour.

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BJA

COMMENTARY

Assessment instruments used during anaesthetic simulation: review of published studies

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This review was undertaken to discover what assessment instruments have been used as measures of performance during anaesthesia simulation and whether their validity and reliability has been established. The literature describing the assessment of performance during simulated anaesthesia amounted to 13 reports published between 1980 and 2000. Only four of these were designed to investigate the validity or reliability of the assessment systems. We conclude that the efficacy of methodologies for assessment of performance during simulation is largely undetermined. The introduction of simulator-based tests for certification or re-certification of anaesthetists would be premature.

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Complex simulation of anaesthesia is an exciting development in medical education and has strong appeal as a way of measuring the performance of anaesthetists without the risks of using real patients.[1] However, 15 yr ago, Vreuls and Overmayer wrote: 'Performance measurement in otherwise sophisticated training simulators is so poorly designed that the measures are virtually useless.'[2] In order to determine how much progress has been made since then we have examined five aspects of the reported assessments to evaluate a simulator-based assessment system.

(i) *The type of simulator.* Chopra[3] developed a classification of simulators that divides simulators into three groups depending upon whether the simulation environment is of high, intermediate or low fidelity.

(ii) *The type of simulation.* A simulator can be used in a full theatre environment with a full complement of staff present, for short simulations with only the anaesthetist present, or as a device for training for specific tasks.

(iii) *The efficacy of the assessment.* Assessment of performance during simulation must be valid and reliable.[4] A valid assessment tests what it is supposed to measure (Table 1). The reliability of a test reflects the consistency and precision of the observations, e.g. between assessors or between tests.

(iv) *The aspects of performance to be tested.* The simulation and assessment must be suited to the aspect of performance being measured. Assessment may be used to measure: propositional knowledge (facts), procedural knowledge, psychomotor skill, decision-making skills and professional behaviour.

(v) *The assessment instruments applied in conjunction with the simulation.* There are a number of measures of outcome that can be used during or after a simulator session (Table 2). These can be directed towards 'single' aspects of performance or they can depend upon a score given for the overall 'global' performance. Multiple instruments may be applied to a single simulation, especially when the sessions are videotaped.

Methods

Search strategy and criteria for assessment of the papers

Articles were sought that described the assessment of performance during simulated anaesthesia and that were published between 1980 and 2000. The review was restricted to articles that had been peer reviewed. Internet search engines were used to search for anaesthesia simulation sites and identify key workers in the field. The Medline and Embase databases were then searched using the words 'anaesthesia' and 'anaesthesiology' (in all their variations), 'simulation', 'performance', 'competence' and 'assessment', as well as the names of authors previously identified. The references in each report were examined for relevance to simulation and its associated authors were

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Table 1 Some aspects of the validity of an assessment

Type of validity	Definition/comments
Face validity	A measure of how appropriate the test items are to the purpose of the assessment. Can be determined by the opinion of an expert group.
Content validity	The extent to which a test is representative of the knowledge or skills that have been learned. To have high content validity a test must sample a full range of the learning objectives identified by the curriculum.
Construct validity	The extent to which the assessment reflects the concept that is being tested, e.g. does an IQ test really test 'general intelligence'? Does a simulator assessment assess 'anaesthetic competence'?
Criterion validity	Relates the candidate's performance to established standards of practice.
Concurrent validity	Relates the test performance to the candidate's performance in tests that are believed to assess the same attribute.

Table 2 Measures of outcome for use in conjunction with simulation

Type of assessment	Definition/comments	Performance measure
Debriefing	Written enquiries or interview can be used after simulations.	Single aspect
Simulated 'mortality'	Can be used during simulations where the 'patient' is severely ill and will soon die unless correct treatments are started immediately. If the anaesthetist chooses the correct treatment, the patient lives and the anaesthetist is therefore deemed to be competent.	Global
Time to solve or detect	Represents the time between the onset of the problem and the point at which the anaesthetist identifies or solves the problem.	Global
Observation and scoring systems	These break down the task of treating the patient into a series of actions, each being given weighting. Observers can then evaluate subjects using a check list or score sheet, noting each of the subject's actions and allocating marks to each.	Single aspect
Psychological tests	Observation of the subject's performance in psychological terms.	Global or single aspect

made the basis of a repeat search. This was continued through three cycles. Studies were included only if they included an attempt to measure performance.

Principal findings

The features of the assessments in these reports are shown in Table 3. Gaba and DeAnda[5] studied 19 first- and second-year anaesthesia residents during simulation on the Comprehensive Anaesthesia Simulation Environment (CASE) simulator. Their purpose was to determine the response of anaesthetists to critical incidents. As part of the study they attempted to determine whether there were differences between individual trainees or between experience levels in the rapidity of detection and correction of intra-operative problems. The simulations contained six adverse events. They assessed 'time to detect'; 'time to solve' and adherence to protocols based on accepted resuscitation guidelines. Acceptable actions were classified as either 'compensation criteria' or 'corrective criteria', depending on whether they merely reduced the consequences of the problem or treated the cause. Deviations from the protocols were classified as 'major' or 'minor'. The investigators showed that second-year residents corrected problems significantly more quickly than first-year residents ($P<0.05$) but that variations in performance were wide. 'Time to detect' and rates of adherence to protocols did not vary between the two groups studied.

DeAnda and Gaba[6] studied eight experienced anaesthetists during the same simulation that had been used with trainee anaesthetists in the study above. The outcomes for the experienced anaesthetists were compared with those previously obtained from learners. There was a trend for earlier detection of the problems and this reached statistical significance during some of the critical incidents. Again, the main finding was of marked variability in performance.

Howard and colleagues[7] used simple written questions to assess the understanding of Anesthetic Crisis Resource Management (ACRM) principles before and after a training course, using a high-fidelity theatre-type simulator (TTS). They showed that residents improved their scores after the simulation, but experienced practitioners did not.

Gaba and colleagues[8] reported a study with the primary purpose of evaluating the inter-rater variability of a system of scoring the behaviour and technical performance of anaesthetists during simulations. They retrospectively reviewed videotapes of 72 participants in ACRM courses. Each subject was rated by five observers for crisis management behaviour and by three observers for technical actions. The study showed that, for technical actions, agreement between observers was good, whereas that for crisis management skills was less good.

Schwid and O'Donnell[9] studied 30 anaesthetists during simulations using the Anaesthesia Simulator Consultant (ASC), a screen-based simulation programme. The purpose of the study was to 'assess the ability of anaesthetists to recognise diagnostic clues, to make the diagnosis rapidly, and to evaluate the patient's response during simulated critical incidents'. Each subject was tested for five simulations. Performance was assessed by adherence to management protocols and rated as either 'correct' or 'incorrect'. There was no consistent relationship between experience

Table 3 Summary of the studies. hi-fi=high fidelity; NS=not stated; PSRA=post-stimulation written answers; TTS=theatre-type stimulator

Ref.	No. of subjects	Type of simulator	Was main aim to investigate efficacy of assessment?	Assessment method					Aspect of performance		Assessments investigated			Comments
				PSRA	Protocol	Simulated mortality	Time to solve or detect	Observation of response	Procedural knowledge	Clinical judgement	Behaviour	Reliability	Construct validity	
5	19	hi-fi TTS	no		yes		yes		yes	yes				Second-year residents corrected problems significantly more quickly than first-year ones.
6	8	hi-fi TTS	no		yes		yes		yes	yes				Repeat of the above protocol with more experienced anaesthetists established a trend towards better performance with experience.
7		hi-fi TTS	no	yes					yes					No attempt to rate subjects during simulation.
8	72	hi-fi TTS	yes		yes				yes	yes	yes	yes	yes	Scoring performance at crisis management by technical and behavioural ratings. Good inter-rater reliability for technical but not behavioural scores.
9	30	screen based	no		yes			yes	yes					Showed relationship between adherence to ACLS protocol and time since training. Did not show increased adherence with seniority.
10	16	intermediate fidelity TTS	no			yes	yes		yes	yes				Anaesthetists with <1 yr of experience took longer to solve and had higher 'mortality'.
11	36	intermediate fidelity TTS	no			yes	yes		yes	yes				Anaesthetists with <1 yr of experience took longer to solve and had higher 'mortality'.
12	28	hi-fi TTS	no				yes	yes	yes	yes				Complex scoring of videotaped sessions in an attempt to make sense of observations.
13	80	intermediate fidelity TTS	no		yes				yes					Showed poor adherence to protocol.
14	10	hi-fi TTS	yes					yes				yes		Designed to measure inter-rater reliability of test.
15	25	hi-fi TTS	yes					yes	yes	yes			yes	Large variation in performance of individuals addressing five different problems.
16	89	hi-fi TTS	no		yes				yes					Showed that ACLS-trained subjects adhered to protocol better than untrained subjects.
17	24	hi-fi TTS	yes		NS		NS	NS	yes		yes	yes	yes	The criteria for assessment and the scores were not made clear.

and performance. The major finding was a clear relationship between the ability of subjects to follow Advanced Cardiac Life Support (ACLS) guidelines and the period of time since ACLS training. No attempt was made to validate the assessment protocol.

Byrne and colleagues[10] published a study using the Anaesthetic Computer-Controlled Emergency Situation Simulator (ACCESS) system, an intermediate-fidelity TTS. The simulations were short scenarios containing simple problems with well-defined solutions. Performance was assessed by 'time to solve' and 'mortality'. The inexperienced subjects took longer to solve the problems and mortality was higher, but this was a preliminary study and no conclusions about the efficacy of the performance assessment were drawn from the documented data.

In 1997, Byrne and Jones[11] studied more anaesthetists using the same technique as in the previous study. The anaesthetists were divided into four groups depending on the length of their anaesthetic experience. Anaesthetists with <1 yr's experience took longer to treat the problem and caused more 'deaths'. Although the result was statistically significant, there were wide variations in performance within each group.

Chopra and colleagues[12] studied the performance of 28 trainee anaesthetists over two simulations using a high-fidelity TTS, the Leiden Anaesthesia Simulator. The purpose of the study was 'to quantitatively evaluate the efficiency of simulation as a training tool in anaesthesia'. Subjects were asked to solve a crisis 4 weeks after being challenged with either the same crisis or a control unrelated emergency. Measurement of performance was based on a scoring system developed from accepted guidelines. Numerical weightings were assigned to each appropriate action as well as a judgement as to whether the action was of major or minor importance. For each individual, a 'treatment score' represented the total score for positive actions, a 'deviation score' represented the total of actions omitted and a 'total performance score' was calculated from the difference between the two scores. The time taken to 'first response' was also noted. For all four measured variables, performance during the simulation of malignant hyperthermia was significantly better in the group exposed to a training simulation of malignant hyperthermia, when compared with their baseline performance.

Lindekaer and colleagues[13] studied performance in managing ventricular fibrillation. Eighty anaesthetists worked in 40 teams of two people during a simulation session of the SOPHUS simulator, a high-fidelity TTS. The simulator sessions were videotaped and reviewed along with the subjects. The performance of each team was compared with the European Resuscitation Guidelines, modified for an anaesthetized patient. The number of teams making each intervention and the times taken from the onset of arrhythmia were noted for each team. There was poor adherence to the resuscitation protocol.

Devitt and colleagues[14] studied the inter-rater reliability of two anaesthetists who independently observed and scored a total of 30 clinical problems. Five problems were generated in each hour-long scenario. For each problem, the actions of the subject were rated as: 0, no response; 1, compensatory intervention; 2, corrective treatment. The two raters were in complete agreement over the score in 29 out of 30 problems. The authors report this as demonstrating a high level of inter-rater reliability.

In 1998, Devitt and colleagues[15] described a study primarily designed to test the items in a rating system developed specifically to evaluate the performance of anaesthetists in a simulated system. The principal objective of the study was to determine whether the test used was reliable as judged by the internal consistency between test items. A secondary item was to see whether the test item could discriminate between two groups of anaesthetists with different lengths of experience. This would demonstrate that the test had construct validity. They studied the performance of 25 anaesthetists during a 1 h simulator session. The inter-rater reliability of the scoring system had been evaluated previously.[14] The more experienced anaesthetists produced significantly higher scores (P<0.001). Individuals did not score consistently across all five scenarios, i.e. there was poor internal consistency between test items. This variation was mostly in two items and when these items were removed from each scenario the consistency was improved.

In 1998, Kurrek and colleagues[16] studied the performance of 89 anaesthetists during a simulation, on a high-fidelity TTS, that contained an episode of ventricular fibrillation. Performance was rated on a three-point scale. Seventy per cent of participants had taken an ACLS course and these subjects achieved higher scores than those who had not been trained (P<0.05). The assessment was limited to measuring adherence to resuscitation guidelines in a small part of a lengthy simulation.

Morgan and Cleave Hogg[17] reported a pilot study of an assessment of medical students who undertook the anaesthetic management of simulated patients in a high-fidelity TTS. Six 15 min scenarios were developed and each student worked through one of these. Each student's performance was videotaped and five evaluators separately assessed it using standardized performance evaluation criteria. The authors do not explain how their scoring system operated. The simulator scores showed high inter-rater reliability. The simulator marks showed poor correlation with marks allocated for the clinical attachment and short answer questions.

Discussion

All the reports reviewed described assessment of performance in the course of conducting a simulated general anaesthetic during which critical incidents were presented.

What aspect of performance was tested?

No study directly assessed propositional knowledge. All the studies made some assessment of procedural knowledge using several assessment techniques: (i) compliance with a recognized treatment algorithm, e.g. ALS;[5 6 8 9 13–16] (ii) compliance with criteria determined by the researchers as representing good practice;[5 6 8 10 11–15 17] (iii) compliance with management systems developed for dealing with anaesthetic crises;[7 8] (iv) complex observations with associated scoring systems;[7–9] and (v) clinical judgement and decision making were assessed in several studies by the measurement of 'time to respond' or 'time to solve'.[5 6 10 11] The study by Gaba and colleagues[8] included assessment of professional behaviours in the form of crisis management scoring. None of these investigations specifically assessed psychomotor skills.

Assessment instruments used

In many of these studies scoring was by review of videotapes.[5 6 8 12 14–17] A number of workers used measures of 'time to solve' or 'time to detect'.[5 6 10 11] Byrne and colleagues used 'patient death' as a measure of outcome.[10 11] Psychological tests have been used in the operating room to measure the performance of anaesthetists.[18 19] There are no reports of this form of assessment being used in conjunction with anaesthetic simulation.

The efficacy of assessments used in the simulator

In this review we have found only four studies that were designed primarily to investigate aspects of the validity and reliability of assessments undertaken in the simulator.[8 14 15 17]

Validity

None of the studies attempted to prove the face or content validity of their assessments. These aspects of the assessments cannot be taken for granted. The construct validity of the assessment system was investigated directly by Devitt and colleagues[15] in a small study of 25 subjects. The individual test items showed poor internal consistency such that conclusions cannot be made about the performance of individuals. Few of these papers make reference to criterion validity, i.e. the extent to which the subject's performance is judged adequate. They record the performance of individuals but do not attempt to transfer this into a measurement of competence. The raters in the study by Gaba and colleagues considered some of the performances 'deficient' if two of the observers considered that the subjects had omitted two actions that the simulator crew had rated as essential.[8] Other studies do not identify any reference criteria for marking a performance as unsatisfactory.

Morgan and Cleave-Hogg[17] discovered poor correlation of their simulator assessment with either written tests or the opinions of supervising consultants. The authors suggest that their new test measures different aspects of their students' performance.

A number of studies found that individual test subjects had a wide variation in response to apparently similar test items.[5 6 10 11 15 16] This can be explained as lack of concurrent validity in the assessment system. It is well recognized with other assessment systems, such as multiple choice questions, that apparently well designed questions can lead to unpredicted responses.[4] These questions are usually discarded. It must be presumed that a similar situation exists in simulator assessments.

Reliability

Devitt and colleagues[14] investigated the inter-rater reliability of scoring. Gaba and colleagues,[8] using three raters, showed good inter-rater reliability in scoring technical actions. There was less inter-rater agreement between five raters scoring ACRM behaviours (such as orientation to case, communication, feedback, anticipation, etc.). The authors analyse the statistics of inter-rater reliability in depth and note that their scoring system requires further development before it can be used for assessment of competence in high-stakes situations such as certification. Morgan and Cleave-Hogg[17] found that the inter-rater reliability of their assessment in 25 subjects was good.

Thirteen reports include comparative assessment of subjects working in anaesthesia simulators. In two of these the construct validity of the assessment is addressed[16 17] and in three measures are described that attempt to determine the inter-rater reliability of the assessment.[8 14 17] (i) Simulators can generate a variety of tasks that can be used as the basis for the assessment of performance. (ii) Simulators can be used to measure adherence to protocols. (iii) There is some preliminary evidence that scoring actions in response to simulated situations appears to show inter-rater reliability. The validity of observations is not established. (iv) The reported within-subject and within-group variability calls into question some of the stimulus–response expectations of the investigators. (v) Attempts to assess the performance of anaesthetists are in their infancy and few of the studies to date have specifically designed assessment to address the questions of validity and reliability. It must be concluded that any moves towards using performance in administering simulated anaesthesia, as assessment in training or in recertification procedures are premature.

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Pulmonary artery catheterization and mortality in critically ill patients

Editor—We read with interest the paper by Murdoch and colleagues.[1] We would like to draw attention to problems with the study design which render the results and conclusions unreliable, but which were not mentioned in the accompanying editorial.[2]

When studying the effects of any medical intervention, the outcomes for patients who receive the intervention are compared to a control group. Variables measured on patients in both groups prior to the start of treatment (and hence which are unaffected by treatment) are termed covariates. For example these may be age, sex, diagnosis, or severity of illness. The main reason for randomly assigning treatment in a randomized controlled trial is to balance covariates between the treated and control groups.[3] In an observational study such as that performed by Murdoch and colleagues, where treatments are not assigned at random, covariates may not be balanced between the intervention and control groups and this needs to be adjusted for during the analysis stage. For example, if an intervention is performed more frequently in patients who have a high probability of death than in those who have a low probability of death, an unadjusted comparison of deaths in those receiving and those not receiving the intervention will be misguided, as the higher death rate is likely to be incorrectly attributed to the intervention. This is clearly demonstrated in early retrospective studies of pulmonary artery catheterization (PAC) in acute myocardial infarction where catheters were predominantly inserted in those patients with congestive heart failure or cardiogenic shock, with the inevitable result that the patients with pulmonary artery catheters had a higher mortality.[4] The propensity score is an attempt to adjust for an imbalance between covariates in the intervention and control groups. It is calculated as the probability that a subject will receive the intervention, given the known set of covariates for that subject. Estimating this probability allows the creation of a 'quasi-randomized experiment'.[5] In other words, if two subjects are found who have the same propensity score, and one of them received the intervention but the other did not, then they can be considered to have been randomly assigned to each group (i.e. they had an equal likelihood of getting the intervention or being a control), and the analysis can proceed. In contrast to randomization which balances both known and unknown covariates, propensity scoring only balances known intervention that have been used during its calculation. If other (unused) covariates exist which influence the decision to provide an intervention, the groups may not be balanced for these. If these covariates are independently related to outcome, results obtained after adjustment using this propensity score will be incorrect. It is therefore vital to include in the calculation of the propensity score all covariates that are related to both the provision of the intervention and also to outcome.

From the above it can be seen that there are three problems with the analysis used by Murdoch and colleagues. First, little attempt was made to investigate if there were other covariates related both to the decision to use PAC and also to the outcome. In the original study of PAC using propensity scores, Connors and colleagues[6] investigated which covariates had most influence on clinicians' decisions to use PACs by asking seven different clinicians to list the factors involved in the decision, and checking this list with a further 13 independent clinicians. All these covariates were used in the construction of their propensity score. In addition, Connors carefully checked for the magnitude that missing covariates would have to have to alter the result by a defined amount using two statistical techniques. The study by Murdoch used an entirely different method. The covariates entered into the logistic regression analysis to determine the propensity score were apparently selected solely on the basis that they were available in the database and some covariates that self-evidently should have been included (e.g. diagnostic group) were not. No checks were made for the effects of missing covariates. It is entirely possible that the Leeds database simply does not contain enough information to produce an accurate propensity score based on all the pertinent covariates.

Second, Murdoch used variables from both before and after PAC to construct the propensity score. The value of some variables recorded following PAC will almost certainly be dependent on the catheter being present. If vasoactive drug use prior to PAC use influenced the decision to provide PAC then these covariates should be used in the propensity score. However, if the decision to use these drugs was made on the basis of readings from a pulmonary artery catheter, they become a surrogate marker of the presence of a pulmonary artery catheter. When surrogate markers are included in regression equations to predict the use of the catheter the equations are, of course, highly but spuriously predictive. Thus the calculation of propensity score to predict an intervention must not contain variables that depend on the intervention. Rosenbaum and Rubin, in one of the core papers on propensity scores, clearly state that measurements should be made prior to treatment assignment.[7]

In statistical parlance, the reason measurements must be made prior to treatment assignment is as follows: the central question is to estimate the average effect on the outcome variable Y of treatment 1 *versus* treatment 2 for the relevant population. Considering the relevant population as a random sample of the entire population under scrutiny, the estimate of this effect is the average value of the appropriate difference between the conditional expectation of the outcome variable Y on the set of predictors in the two treatment groups. Therefore the predictors used to make assignment decisions must be recorded before the intervention takes place, then the expectation of outcome in each group is estimated (conditional on the predictors in each treatment group). Finally, the average difference between the estimated conditional expectations over the estimated distribution of the predictors is computed. These three steps must be followed carefully to estimate causal effects of an intervention.

Third, a more general point is that non-randomized studies rely on natural variations in patient treatment, in other words, that similar patients are sometimes given an intervention but at other times not. If all patients with the same condition are treated in the same way comparison between a treated and control group cannot be made because the two groups do not co-exist. If PAC was 'protocol driven' in Leeds, as suggested in the manuscript, variations between clinicians would be minimal, and it would not be possible to define the two groups. Lack of natural variation is suggested by the fact that norepinephrine, epinephrine and dobutamine were virtually never used in the control group. This might explain why Murdoch chose not to perform the case-by-case matching analysis undertaken by Connors; with a very skewed distribution of covariates between the control and treatment group it may be very difficult to match patients. A judgement on how much treatment variation existed in Murdoch's data could be made by comparing the number of patients who received a PAC and the number who did not receive a PAC in

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each quintile or other subdivision of the propensity score, though these figures were not provided. Murdoch and colleagues do state that there was no significant difference between the covariates in each quintile except the lowest, though this may have been due to the small number of subjects in each group leading to wide confidence intervals.

We suggest that the majority of conclusions in the paper, and the detailed analysis of the possible reasons for the difference between Murdoch's results and those of Connors in the accompanying editorial, are based on results that are fundamentally flawed and sadly add little to the ongoing debate about pulmonary artery catheters. In particular, the paper provides no supportive evidence for the statement that a randomized controlled trial of PAC would have insufficient power to demonstrate an effect on mortality even with very large numbers of patients. We believe that a randomized trial of PAC is imperative to resolve some of the current uncertainties surrounding their use.

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Editor—The letter by Young and colleagues raises three questions regarding the statistical methods we used in our paper[1] examining the effect of pulmonary artery catheter use on mortality in intensive care patients. We welcome the opportunity to respond and will take their points in turn.

The first point is in regard to choice of variables used in calculating our propensity score. It is true that we did not seek expert opinion in determining factors influencing the clinicians' decision making process with regard to insertion of a PA line. The validity of this technique—asking 'expert' opinion to identify variables which determine practice is questionable—variables are often suggested which in real life are not used. Our database was constructed prospectively to collect data which were determined locally as important in determining patient outcome and in describing haemodynamic manipulation including pulmonary artery catheterization. Within this, our choice of variables to create a propensity score is strongly supported by the area under the curve of the ROC plot. This suggested a more predictive score than that obtained by Connors and colleagues.[2] We agree that there may be covariates missing from our analysis, but in view of the high AUC the effect of such missing covariates is unlikely to be much greater than those in the Connors study. Since the publication of the Connors paper, better approaches to the assessment of the sensitivity of regression results to unmeasured confounders have been developed. Lin and colleagues have shown that the exposure effect and the effects of measured and unmeasured confounders can be formulated through a regression model, allowing inferences about the true exposure effect by making simple adjustments to the point interval estimates.[3] Application of this approach to the Connors study led Lin to recalculate the Connors point estimate for the odds ratio for mortality with a PA catheter as close to unity, and possibly as low as 0.8, a finding very close to the results we have published in our study. Moreover, Connors went on to estimate the magnitude of the effect of a potential confounder on risk of death or chance of allocation to PA catheterization as six-fold before a relative risk of death of 1.0 could be misrepresented as 1.21. However, Lin has pointed out—and Connors confirmed—that the Connors group inadvertently described the odds ratio of death as the probability of death. This led them to overestimate substantially the size of an unmeasured covariate needed to misrepresent a beneficial or zero effect of PA catheterization as an adverse effect, bringing the likely effects into line with the Lin calculation above. This potential effect of small unmeasured covariates may similarly apply to our study.

Diagnostic group was available in our database, but was not included in the propensity score model. This was because diagnosis was unimportant in determining catheter use in comparison with physiological derangement. A single diagnosis can encompass a wide degree of patient illness, while simple diagnostic categories fail to represent the real range of pathophysiological disturbance. By contrast, analysis of Project Impact data has shown that in American intensive care units organizational characteristics are highly significant variables regarding PA catheter use.[4] The presence of full time ICU staff is associated with a two-thirds decrease in catheter use OR 0.36 (95% CI 0.28–0.45); this variable is not included in the Connors study.

The second point raised relates to the use of inotropes to construct the propensity score. We accept that the PA catheter is likely to have influenced the choice of inotrope, and so individual inotropes should not have been included in the model. We are grateful to Young for pointing out this error. We had originally intended analysing only whether or not any inotrope had been used (as a single binary variable) as on our unit inotrope resuscitation is commenced prior to PA catheter insertion and regard as a primary indication for a PA catheter. Recalculating the propensity score with inotropes as a single binary variable results in inotrope use being excluded from the propensity score, but otherwise has little effect on the model, area under the ROC plot, propensity score, or PA catheter predictions of mortality.

The third point raised relates to lack of natural variation between the two groups. Young correctly points out that our 'protocol driven' approach results in a skewed distribution of our propensity score between those receiving and not receiving a PA catheter. Distribution of the number of patients in each quintile is as follows:

quintile 1 PA=44 no PA=751,
quintile 2 PA=155 no PA=627,
quintile 3 PA=321 no PA=464,
quintile 4 PA=588 no PA=205,
quintile 5 PA=726 no PA=61

The proportion of patients in each quintile has similar covariate distribution. This we believe is due to the predictive nature of the propensity score in correctly identifying PA catheter insertion and minimal random treatment—a less skewed distribution would only be achieved if there were a greater random effect in the decision to insert a PA catheter and would undermine a consensus view on decisions for their insertion. This skewedness is not extreme, and is in fact very similar to that in an example by Rosenbaum and Rubin[5] (treatment of coronary artery stenosis shows higher propensity score in the surgical population compared to the medical population) which they deemed 'acceptable'.

Finally, we did not state in our paper that a randomized study should not take place; merely that it would be difficult to carry out and unlikely in our opinion to 'answer' the debate.

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Lymphatic drainage of the thoracic paravertebral space

Editor—Karmakar and colleagues[1] are the latest to report contralateral spread following a thoracic paravertebral injection to relieve the pain of fractured ribs. Injection of bupivacaine 20 ml into a thoracic paravertebral catheter produced an ipsilateral block extending over seven thoracic segments. Iopamidol, a radio-opaque contrast, was then injected into the catheter to confirm placement. Contrast was noted in the ipsilateral paravertebral space and demonstrably spread across the mid-line at T6, at approximately the level of the tip of the catheter. No corresponding contralateral sensory blockade was found nor was there any haemodynamic change, suggesting that spread was not via the epidural space.

Large molecule, water-soluble, radio-opaque contrast media, like Iopamidol, are scavenged by the lymphatic system. The paravertebral space forms a watershed for lymphatic drainage. The bulk is to local nodes and then to tributaries of the thoracic duct. The latter are inconsistent and form a plexiform network lying anterior and lateral to the vertebral bodies.[2] Laterally, extrapleural material is scavenged by the lymphatics of the intercostal space. Some lymphatics from the subpleura join bronchial lymphatics. This may be particularly relevant as spread tends to be from the left hemithorax into the right hemithorax. Classical studies of the movement of bronchogenic tumour cells have shown spread from the left lung across the mid-line through lymphatic bridges which are relatively constant, one of which, notably, is at the T6 level.[3]

Though there is usually little delay in the process of lymphatic drainage of contrast, it is not difficult to envisage a situation of the usual drainage systems and paths of least resistance being disturbed by a primary process such as trauma,[1 4] or a pathological process such as infection and tumour.

We agree that spread of local anaesthetic is likely to have occurred through the lax tissues of the prevertebral fascia as demonstrated in various cadaver studies,[5] but feel that it should not be presumed that contrast media *in vivo* will mimic the spread of local anaesthetic and that a radiological artefact produced by the scavenging of the contrast by the lymphatic system cannot be discounted.

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Acknowledgement

We are grateful to Dr Thomas F Molnar, Head of Department Thoracic Surgery, University Medical School of Pécs, Hungary for information and reference about the spread of malignant cells.

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Editor—Thank you for the opportunity to reply to Nel, Shanahan and Conacher's letter in which they raise the question that the contralateral spread of contrast seen after the paravertebral injection in our patient[1] could have been an artefact produced by scavenging of contrast by the lymphatic system. The correspondents have raised an interesting question, which requires discussion; to our knowledge it has never been addressed in relation to radiocontrast studies in regional anaesthesia.

We agree that the thoracic paravertebral space forms a watershed for lymphatic drainage, and lymphatic vessels on either side of the vertebra anastomose with each other and those from the contralateral side to form a lymphatic plexus along the lateral and anterior surface of the vertebrae.[2] In addition, the subcarinal lymph nodes act as a lymphatic bridge between the two hemithorax providing a pathway for contralateral spread of malignant cells from the left lung.[3]

Any foreign material, contrast in our case, injected interstitially may be taken up by the lymphatic capillaries after which it is transported with the lymph to the regional lymph nodes and phagocytized. The exact mechanism involved in uptake by the lymphatic capillaries is not known but passage through the endothelial junctions and/or pinocytosis through the cells are thought to be involved,[4] and depend on the size and the number of particles injected.[4] Small diameter particles (less than a few nanometers) are mostly exchanged through the blood capillaries; larger particles (diameter, a few tens of nanometers) are absorbed by the lymphatic vessels; and particles which are hundreds of nanometers in diameter are trapped in the interstitial space for a long time.[4] Iopamidol, as acknowledged by Nel, Shanahan and Conacher, is a large molecule and so may not be so readily or rapidly taken up by the lymphatic vessels. Moreover, due to the low pressure in the lymph vessels,[5] there is usually some delay before the absorbed contrast appears in a regional lymph node where it is filtered and scavenged by the macrophages.

In our report, the anteroposterior chest x-ray demonstrating contralateral spread was taken immediately after the contrast injection,[1] which takes about 1–2 min. Moreover there are no suggestions from the pattern of contrast spread that it occurred via the lymphatics, as the opacified lymphatic channels would appear as thin continuous lines of contrast.[6] Even if trauma related changes resulted in accelerated uptake by the lymphatics as suggested by the correspondents, within the time frame that the chest x-ray was taken this would be negligible and unlikely to produce the demonstrated radiological images. A CT scan would have been ideal to demonstrate the physical spread to the contralateral side.[7]

Based on the above facts, and the wealth of evidence demonstrating contralateral spread after thoracic paravertebral injection in cadavers[8] and *in vivo*,[1 9] with[9] or without[1] contralateral anaesthesia, we still believe that physical spread via the subserous layer of connective tissue contributed to the contralateral spread of contrast in our patient.[1]

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Anaesthetic management of lobectomy for lung abscess or bronchopleural fistula

Editor—We read with interest Pfitzner and colleagues' account of the anaesthetic management of a patient requiring lobectomy for a cavitating lung abscess complicated by haemoptysis.[1] We have previously described our ventilatory management of a 36-yr-old patient with a bronchopleural fistula complicating necrotizing group A β-haemolytic streptococcal pneumonia[2] and we feel the technique we described provides an alternative approach to such patients.

Whilst mechanically ventilated on the intensive care unit, our patient developed a large air leak (500 ml per 800 ml tidal volume), and adequate ventilation became impossible. Her underlying pneumonia was complicated by generalized acute lung injury in the non-pneumonic areas of her lungs resulting in profound hypoxaemia. Under fibrescopic guidance, we placed a single 2 ml size 7F Fogarty embolectomy catheter alongside the single lumen tracheal tube sequentially into the right intermediate, lower and then middle lobe bronchi. After placement in the right middle lobe bronchus, the balloon was inflated and there was almost complete cessation of the air leak. Effective ventilation of all other lung segments was continued. Using this technique we confirmed the presence of a bronchopleural fistula affecting solely the right middle lobe.

During her subsequent middle lobectomy she was ventilated using a left-sided double lumen tracheal tube with a size 7F Fogarty catheter placed via the tracheal lumen of the tracheal tube into the right middle lobe bronchus. Attempted single left lung ventilation, to improve surgical access, resulted in rapid arterial desaturation to Sa_{O_2} 65% which was attributed to the on-going acute lung injury in the non-pneumonic areas of lung. Ventilation of the left lung and the right upper and lower lobes with selective blockade of the middle lobe using the Fogarty catheter as a bronchial blocker maintained saturations of 94–96%. Right middle lobectomy was performed and the patient eventually made a full recovery.

We published this case report[2] because we felt that this technique of bronchial blockade, previously described by other authors,[3 4] has a useful role in the ventilatory management of patients who require isolation of particular lobes for a variety of reasons. Our patient had severe necrotizing middle lobe pneumonia complicated by bronchopleural fistula and could not be adequately oxygenated by one-lung ventilation due to coexistent generalized pulmonary dysfunction. We feel that the technique of selective bronchial blocking is worth considering in this difficult group of patients.

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1 Pfitzner J, Peacock MJ, Tsirgiotis E, Walkley IH. Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung. *Br J Anaesth* 2000; **85**: 791–4
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Fogarty embolectomy catheter for selective bronchial blockade. *Intens Care Med* 1999; **25**: 535–7

3 Campos JH. Effects on oxygenation during selective lobar versus total lung collapse with or without continuous positive airway pressure. *Anesth Analg* 1997; **85**: 583–6

4 Campos JH, Ledet C, Moyers JR. Improvement of arterial oxygen saturation with selective lobar bronchial block during haemorrhage in a patient with previous contralateral lobectomy. *Anesth Analg* 1999; **81**: 1095–6

Editor—We are grateful for the opportunity to comment on McCormick and Wilson's letter, which describes the management of a very different patient from ours.[1] Their patient with group A β-haemolytic streptococcal pneumonia, ARDS and a bronchopleural fistula with a large air leak, was already being mechanically ventilated at the time that right middle lobectomy was performed.[2] To achieve adequate ventilation and oxygenation pre- and intra-operatively, two-lung ventilation with selective blockade of the right middle lobe bronchus with a Fogarty catheter was required, and they are to be congratulated on achieving a successful outcome in this very sick patient.

In patients with a cavitating lung abscess and otherwise reasonably healthy lungs, a safer management plan in our view involves: first, prompt lung separation to prevent contamination of the good lung; and second, refraining from ventilating the lung with the abscess until the lobectomy is complete and the airway cleared by bronchial suction.[1] If ambient pressure oxygenation[3,4] is applied to an operated lung from which nitrogen has been excluded, there will be little risk of marked arterial desaturation in the vast majority of cases. However, this management plan would be inappropriate for a patient with ARDS, since single-lung ventilation would almost certainly be associated with an appreciable degree of shunting through both the ventilated and the non-ventilated lungs.

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1 Pfitzner J, Peacock MJ, Tsirgiotis E, Walkley IH. Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung. *Br J Anaesth* 2000; **85**: 791–4

2 McCormick BA, Wilson IH, Berrisford RG. Bronchopleural fistula complicating group A β-haemolytic streptococcal pneumonia. Use of a Fogarty embolectomy catheter for selective bronchial blockade. *Intens Care Med* 1999; **25**: 535–7

3 Pfitzner J, Peacock MJ, Daniels BW. Ambient pressure oxygen reservoir apparatus for use during one-lung anaesthesia. *Anaesthesia* 1999; **54**: 454–8

4 Baraka A, Lteif A, Nawfal M, *et al.* Ambient pressure oxygenation via the nonventilated lung during video-assisted thoracoscopy. *Anaesthesia* 2000; **55**: 602–3

Effects of isoflurane, sevoflurane and propofol on jugular venous oxygen saturation

Editor—Nandate and colleagues recently reported the results of their study of the effects of isoflurane, sevoflurane and propofol on jugular venous oxygen saturation.[1] We write to express our concerns about the technique used for induction and maintenance of anaesthesia in the propofol group.

Our concerns are based upon a report by Vuylsteke and colleagues (from the same institution) of a high incidence of amnesic awareness associated with this technique.[2] In the earlier study, anaesthesia was induced with midazolam 50 $\mu g\,kg^{-1}$ and fentanyl 12 $\mu g\,kg^{-1}$, and maintained with a propofol infusion. Using the isolated forearm test for 45 min after induction, it was found that four of the five subjects responded to command, leading the authors to conclude that: 'The use of amnesic drug will avoid a conscious recall but patients who experienced amnesic awareness may suffer from post-traumatic disorder. A midazolam–fentanyl induction does not prevent amnesic awareness and should be abandoned.'[2] As far as we are aware, this statement has not been retracted. In the propofol group of the current study midazolam 100 $\mu g\,kg^{-1}$ and fentanyl 15 $\mu g\,kg^{-1}$ were used, but there is no evidence that these doses prevent awareness. It is unclear why this technique has not been abandoned.

In both studies a morphine premedication was used and anaesthesia was maintained with a propofol 3 $mg\,kg^{-1}\,h^{-1}$ infusion. We used the TIVA Trainer, a computerized pharmacokinetic simulator (©F Engbers, The Netherlands) to estimate the drug concentrations this regimen will produce 45 min after induction of anaesthesia, when skin incision and sternotomy are likely to occur. In a 70 kg male, the estimated blood concentrations will be propofol 1.2 $\mu g\,ml^{-1}$, fentanyl 3.5 $\eta g\,ml^{-1}$ and midazolam 43 $\eta g\,ml^{-1}$. These concentrations may be sufficient to prevent memory of events at this stage, as it has been shown that in healthy volunteers the Cp50 for loss of memory for words is 0.62 $\mu g\,ml^{-1}$ for propofol and 56 $\eta g\,ml^{-1}$ for midazolam.[3]

However, it is less certain that this combination is adequate to prevent response to command or awareness. Kazama and colleagues studied the interaction between fentanyl and propofol during abdominal surgery.[4] Using their graphs, it is evident that a combination of propofol 1.2 $\mu g\,ml^{-1}$ and fentanyl 3.5 $\eta g\,ml^{-1}$ is *below* the Cp50 for somatic and haemodynamic responses to skin incision, peritoneal incision, and abdominal wall retraction.

Russell has said that a benzodiazepine/opiate technique can at best be said to provide 'general amnesia' and not general anaesthesia.[5] For the first 45 min of the current study, while the blood propofol concentration was slowly increasing from zero, the authors relied on the (decreasing) midazolam and fentanyl levels to maintain unconsciousness. Lack of recall does not necessarily imply adequate anaesthesia. Had they chosen to look for it, the authors may well have found that many of their subjects responded to command during this period.

Is anaesthesia adequate if the patient responds to command, but later shows no sign of recall? Some anaesthetists may feel it is, while others are unsure.[6] The comments of Vuylsteke[2] and Russell[5] seem to indicate that they feel that response to command may indicate inadequate anaesthesia. Until this issue is resolved we feel that if a study involves an anaesthetic technique that relies on a benzodiazepine/opiate combination to provide unconsciousness, the investigators should seek and report clinical signs of awareness. Tests for post-operative recall and adverse psychological sequelae should also be performed.

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1 Nandate K, Vuylsteke A, Ratsep I, *et al.* Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery. *Br J Anaesth* 2000; **84**: 631–3

2 Vuylsteke A, Djalani G, Kneeshaw J, Bethune DW. Amnesic awareness during cardiac surgery: comparison of three different regimens. *Br J Anaesth* 1996; **76** (Suppl 2): A81

3 Veselis RA, Reinsel RA, Feshchenko VA, Wronski M. The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. *Anesthesiology* 1997; **87**: 749–64

4 Kazama T, Ikeda K, Morita K. The pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses to skin incision, peritoneum incision, and abdominal wall retraction. *Anesthesiology* 1998; **89**: 894–906

5 Russell IF. Midazolam-alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *Br J Anaesth* 1993; **70**: 42–6

6 Andrade J, Jones JG. Is amnesia for intraoperative events good enough? *Br J Anaesth* 1998; **80**: 575–6

Editor—We certainly share the concerns raised by Absalom and Miles and have indeed not retracted our findings published in 1996. We would like, however, to point out that: our small study conducted in 1996 and published as an abstract has never reached the status of peer-reviewed publication due to the small sample size; as pointed out by Absalom and Miles, the anaesthetic technique used in the present study was different with a dose of midazolam twice as high as previously described and a slightly higher dose of fentanyl; and, the time elapsed between induction (and initiation of the propofol infusion) and skin incision was longer in the present study because of the insertion of a retrograde jugular bulb catheter.

Anaesthetic regimen used in cardiac anaesthesia have to compromise between anaesthesia and haemodynamic stability. The aim of our study was to compare three different anaesthetic regimen that are currently used. In the absence of monitoring that would allow us to detect 'amnesic awareness', we felt that we were not diverging from what is still considered standard and safe practice. None of the patients, who were all reviewed post-operatively, spontaneously reported any recall of their surgery.

B. F. Matta
A. Vuylsteke
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Adult epiglottitis: an under-recognized, life threatening condition

Editor—I read the case reports from Ames and co-workers with interest, and some surprise. Was case 1 really epiglottitis? The description of the case does not comment on the appearance of the epiglottis, other than the mass. The symptoms recorded are suggestive of laryngeal obstruction, and would appear to be confirmed by the clinical findings of a mass rather than a diffusely swollen, hyperaemic epiglottis, typical of the epiglottitis described in the other two cases.

The authors state that there are no reports linking epiglottitis with the smoking of heroin. The presentation of heroin users with systemic candidiasis is well described, however. The most common presentations are with endophthalmitis, or cutaneous or osteoarticular manifestations,[1–3] and infection has been attributed to contamination of the lemon juice, used as a dilutent for the heroin, with *Candida albicans*. Perhaps in this case it was the isolation of Candida that was more relevant than the epiglottitis?

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1 Shankland GS, Richardson MD, Dutton GN. Source of infection in candida endophthalmitis in drug addicts. *BMJ* 1986; **292**: 1106–7

2 Collignon PJ, Sorrell TC. Disseminated candidiasis: evidence of a distinctive syndrome in heroin abusers. *BMJ* 1983; **287**: 861–2

3 Newton-John HF, Wise K, Looke DF. Role of lemon in disseminated candidiasis of heroin abusers. *Med J Aust* 1984; **140**: 780–1

Editor—May I congratulate Ames and colleagues on their recent reminder that adult epiglottitis is under-recognized and potentially lethal.[1] A few years ago, Stuart and Hodgetts made similar points in the *British Medical Journal*.[2] Like all important messages, it bears repetition to each new generation of doctors, since epiglottitis can progress from being no more than a bad sore throat to total airway obstruction within a few hours.

I fully agree with Ames that an airway needs to be established as soon as the diagnosis is made, even if airway obstruction appears minimal. I agree also that the performance of a tracheostomy under local analgesia is unwise, since patients with epiglottitis find it easier to breathe sitting up rather than lying down. The key question is, how does one intubate these patients safely? Breathing the patient down with an inhalational technique can lead to acute loss of the airway, as happened in case 3 of Dr Ames's paper and also to one of my patients.[3] The solution, I believe, is to perform a cricothyroidotomy under local analgesia and insuffate oxygen into the lungs via a mini-tracheostomy tube or equivalent *prior* to inducing general anaesthesia with intravenous agents and succinylcholine. In the event of a difficult intubation, the patient can be kept well oxygenated by this route until a tracheostomy is performed.

With regard to the issue of tracheostomies, I would query whether they are necessary once the patient has been safely intubated. Adult epiglottitis normally resolves within 24–48 h once antibiotics have been started. It seems unnecessary to subject a young patient to the long-term complications of tracheostomy, such as tracheal stenosis, when the alteration is a day or two on the intensive care unit attached to a ventilator.

W. Konarzewski
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1 Ames WA, Ward VMM, Tranter RMD, Street M. Adult epiglottitis: an under-recognized, life-threatening condition. *Br J Anaesth* 2000; **85**: 795–7

2 Stuart MJ, Hodgetts TJ. Adult epiglottitis; prompt diagnosis saves lives. *BMJ* 1994; **308**: 329–30

3 Konarzewski WH. Adult epiglottitis: heightened awareness saves lives. *BMJ* 1994; **308**: 719

Editor—I thank Sherrard and Konarzewski for their interest in our case reports.[1] Despite Dr Sherrard's comments regarding case 1, I firmly believe that the diagnosis of 'epiglottitis' was correct. The symptoms, signs and radiological investigations are compatible with the diagnosis. Furthermore, while the swollen epiglottis completely obscured the larynx, fibreoptic examination demonstrated diffuse swelling of the aryepiglottic structures which is characteristic of the adult form of the disease (Figure 4 in the article).

I appreciate Dr Sherrard's comments regarding lemon juice as a carrier medium for Candida. Lemon juice is used to dissolve street heroin before its intravenous use.[2] Although the patient was not directly questioned as to how he prepared this drug, it is unlikely that he first dissolved it in lemon juice prior to smoking it. As detailed in our discussion, the causal organism or precipitant of epiglottitis in adults is often difficult to identify. While we were unable to determine definitively the aetiology of epiglottitis in this case, the most likely causes were considered to be fungal or thermal epiglottitis. The direct effects of heroin inhalation as a causative factor is unlikely as diacetylmorphine has been found to be fungicidal.[3]

I am grateful to Dr Konarzewski for emphasizing the key issues in our article. I agree that *an* alternative and safe course of action would include an awake cricothyroidotomy prior to inducing anaesthesia and securing the airway. The technique is well described and associated with few complications.[4] However, although not typically the case in these patients, tracheal intubation may be difficult and a tracheostomy would then become necessary. In case 1, although the patient was intubated, he underwent a tracheostomy because the diagnosis was initially uncertain and the epiglottitic mass required further evaluation. The trachea was decannulated 9 days after the original presentation. In retrospect, case 2 may well have been managed without proceeding to a tracheostomy. At the time, however, with the difficulty in establishing an airway, it was considered the safest course of action to provide and maintain a stable airway. Lastly, in case 3, attempts at tracheal intubation had already failed and a tracheostomy became necessary. I agree however that, in general, a tracheostomy and its concomitant complications are best avoided, but realize this may not always be possible.

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1 Ames WA, Ward VMM, Tranter RMD, Street M. Adult epiglottitis: an under-recognized, life-threatening condition. *Br J Anaesth* 2000; **85**: 795–7

2 Newton-John HF, Wise K, Looke DF. Role of lemon in disseminated candidiasis of heroin abusers. *Med J Aust* 1984; **140**: 780–1

3 Shankland GS, Richardson MD, Dutton GN. Source of infection in candida endophthalmitis in drug addicts. *BMJ* 1986; **292**: 1106–7

4 Ames WA, Venn P. Complications of the transtracheal catheter. *Br J Anaesth* 1998; **81**: 825–9

Post-operative nausea and vomiting—time for balanced antiemesis

Editor—Further to the editorial by Heffernan and Rowbotham,[1] I note there was no mention of low dose midazolam infusion as an option for patients with refractory post-operative nausea and vomiting (PONV). I agree totally with the concept that PONV probably requires a 'balanced approach' for effective treatment of a multifactorial problem.

I refer readers to a recent study examining the effect of midazolam on persistent nausea and vomiting.[2] Low dose infusion of midazolam is thought to decrease dopamine input at the chemoreceptor trigger zone (CRTZ) in addition to decreasing anxiety. It may also decrease adenosine re-uptake. This leads to an adenosine-mediated reduction in synthesis, release and postsynaptic action of dopamine at the CRTZ. In addition to altering adenosine-mediated effects, midazolam probably reduces dopaminergic neuronal activity by binding to the gabba-aminobutyric acid–benzodiazepine complex. The study, although small in numbers, was terminated early due to statistically significant differences between the groups.

On a purely anecdotal level, I have used low dose midazolam infusions for several years and found it to be extremely efficacious, using a regimen of a 1 mg loading dose followed by a $1\ \mathrm{mg\,h^{-1}}$ infusion for an average sized adult. Over-sedation does not appear to be a problem. I feel low dose midazolam infusions are a useful treatment option in the management of refractory PONV.

C. Weidmann
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1 Heffernan AM, Rowbotham DJ. Post-operative nausea and vomiting—time for a balanced antiemesis. *Br J Anaesth* 2000; **85**: 675–6

2 DiFlorio T, Goucke CR. The effect of midazolam on persistent nausea and vomiting. *Anaesth Intensive Care* 1999; **27**: 38–40

Editor—We read with interest Heffernan and Rowbotham's editorial[1] and wish to make some comments. In the literature, there are numerous randomized double-blind controlled studies comparing one antiemetic to another or placebo for prophylaxis of post-operative nausea and vomiting (PONV). Even a meta-analysis of these studies failed to show that any antiemetic is superior in prevention of PONV.[2] A majority of the studies have enrolled patients anaesthetized with a nitrous oxide and a volatile technique.

There has been an increasing trend for inducing and maintaining anaesthesia using a combination of remifentanil and a target-controlled propofol infusion while ventilating the patients with oxygen and air. Omission of nitrous oxide and the use of total intravenous anaesthesia (TIVA) have been shown to be less emetogenic anaesthetic techniques.[3 4]

The neuropharmacology of PONV is now better understood. Multiple receptors including dopaminergic, muscarinic, cholinergic, opioid, histamine, serotonin and NK_1 mediate the emetic reflex.[5] A balanced antiemetic prophylaxis would need to block most or all of these receptors. This may not be a practical approach.

We believe that instead of balanced antiemetic pharmacological prophylaxis, an approach should be considered including the use of less emetogenic anaesthetic techniques and local or regional blocks for good post-operative pain relief. This may reduce the need for perioperative antiemetics.

J. Nunez
A. Mallick
Huddersfield
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1 Heffernan AM, Rowbotham DJ. Post-operative nausea and vomiting—time for balanced antiemesis. *Br J Anaesth* 2000; **85**: 675–7

2 Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000; **90**: 186–94

3 Tramer M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997; **78**: 247–55

4 Tramer M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: metanalysis of intraoperative and postoperative emesis in randomized controlled studies. *Br J Anaesth* 1996; **76**: 186–93

5 Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000; **59**: 213–43

Editor—It is encouraging to see that our editorial is provoking good interest.[1]

Yes, we do acknowledge the fact that midazolam may be used in the treatment of persistent post-operative nausea and vomiting (PONV) by the mechanisms referred to in Weidmann's letter.[2 3] He and other authors refer to the fact that PONV is a multifactorial problem and that it is likely that combination therapy with more than one agent acting via different receptors will be required.[3–7] While the use of midazolam infusions in a small study does appear to significantly reduce the incidence of persistent PONV, it is not a method that can be resorted to lightly. The patients probably need high dependency care and this may not always be available for this patient group. However, in this study the authors have embraced the concept of balanced antiemesis; patients were also given metoclopramide, prochloperazine and droperidol, agents which act at different receptors.[2]

Nunez and Mallick postulate that using total intravenous anaesthesia (TIVA) and omitting nitrous oxide are less emetogenic techniques. We do agree with the authors that more local and regional techniques should be used in practice, which would decrease the incidence of PONV. However, a meta-analysis in 1997 confirms that TIVA studies are documented poorly and there is not enough evidence that it is an anaesthetic technique with a low emetogenic potency.[8] Since then, there has been no convincing evidence for an improvement in PONV with TIVA. One study shows an improvement in PONV but only in the first few hours post-operatively.[9] A second study shows a low incidence of PONV in both TIVA and inhalational anaesthesia groups.[10] Omitting nitrous oxide does not seem to be without its problems.[11] It appears only to decrease significantly post-operative vomiting if the risk of vomiting is high and does not affect nausea or complete control of emesis.

A. M. Heffernan
D. J. Rowbotham
Leicester

1 Heffernan AM, Rowbotham DJ. Post-operative nausea and vomiting—time for a balanced antiemesis. *Br J Anaesth* 2000; **85**: 675–6
2 DiFlorio T, Goucke CR. The effect of midazolam on persistent nausea and vomiting. *Anaesth Intensive Care* 1999; **27**: 38–40
3 DiFlorio T. The uses of midazolam for persistent postoperative nausea and vomiting. *Anaesth Intensive Care* 1992; **20**: 383–6
4 Matson A, Palazzo M. Postoperative nausea and vomiting. Adams AP, Cashman JN, eds. *Recent Advances Anaesth and Analg* 1995; 19: 107–26
5 McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady R. Comparison of ondansetron with ondansetron and dexamethasone in the prevention of postoperative nausea and vomiting. *Anesth Analg* 1994; **879**: 961–4
6 Pueyo FJ, Carroscosa F, Lopez L, Irabarren MJ, Garcia-Pedrajas F, Saez A. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg* 1996; **83**: 117–22
7 Ahmed AB, Hobbs GJ, Curran JP. Randomised, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. *Br J Anaesth* 2000; **85**: 678–82
8 Tramer M, Moore A, McQuay H. Propofol anaesthesia and post-operative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997; **78**: 247–55
9 Brooker CD, Sutherland J, Cousins MJ. Propofol maintenance to reduce postoperative emesis in thyroidectomy patients: a group sequential comparison with isoflurane/nitrous oxide. *Anaesth Intensive Care* 1998; **26**: 625–9
10 Fish WH, Hobbs AJ, Daniels MV. Comparison of sevoflurane and total intravenous anaesthesia for daycase urological surgery. *Anaesthesia* 1999; **54**: 1002–6
11 Tramer M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: metanalysis of intraoperative and postoperative emesis in randomized controlled studies. *Br J Anaesth* 1996; **76**: 186–93

Publications on paediatric anaesthesia

Editor—I read with interest the review by Brambrink and colleagues.[1] It confirms earlier observations on the low *per capita* output of German anaesthesiology.[2–5] This is true in comparison with the major English speaking and Scandinavian countries, and also with Switzerland and Austria. It was interesting to read that, at least in the field of paediatric anaesthesia, this is still the case if non-English language journals are included, considering a recent controversy on this point.[6–8]

Brambrink and colleagues made a mistake, however, concerning the names and database coverage of two German anaesthesia journals in Table 5. *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* (*AINS*) is indexed in Medline, but was **NOT** listed in the *Journal Citation Report* for the years analysed by Brambrink (1993–1998). It was only in 1999 that it was included for the first time under the abbreviation *Anasth Intensiv Notf* with an impact factor of 0.473. Consequently, *AINS* has no known impact factor for the years 1993–1998. Brambrink was probably misled by the abbreviation *Anasth Intensivmed* in the *Journal Citation Report* that stands for *Anästhesiologie & Intensivmedizin* (*A&I*), another German journal which is included in the Science Citation Index, but **NOT** in Medline. The mean impact factor of *A&I* for the years 1993–1998 is only 0.426, not 0.690 as given by Brambrink as it achieved an impact of 0.692 only in 1997 but was ranked lower for all other years.[9]

In the context of the methods used by Brambrink of counting only Medline-indexed publications and assigning an impact factor of zero to journals not listed in the journal citation reports 1993–1998, publication in *A&I* do not count at all and publications in *AINS* have no impact factor.

As 20 of the 22 paediatric articles in *AINS* were from Germany, this influences the country rankings in Tables 6 and 7 of Brambrink's paper. The already low total impact factor of Germany shrinks further from 88.38 to 74.58 and the mean impact factor from 0.875 to 0.738, making it even clearer that German paediatric anaesthesia in the mid-1990s was far behind its major competitors.

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1 Brambrink AM, Ehrler D, Dick WF. Publications on paediatric anaesthesia: a quantitative analysis of publication activity and international recognition. *Br J Anaesth* 2000; **85**: 556–62
2 Carnie J, Kumar B. An analysis of thirty years of contributions to the British anaesthetic literature (1953–1982). *Br J Anaesth* 1984; **56**: 1171–4
3 Schubert A, Glänzel W, Braun T. Scientometric datafiles. A comprehensive set of indicators on 2649 journals and 96 countries in all major science fields and subfields. *Scientometrics* 1989; **16**: 3–478
4 Pomaroli A, Hauffe H, Benzer A. Who publishes in the large anaesthesia journals? *Br J Anaesth* 1994; **72**: 723–5
5 Boldt J, Maleck W, Koetter KP. Which countries publish in important anesthesia and critical care journals? *Anesth Analg* 1999; **88**: 1175–80
6 van Aken H, Prien T. Forschungsqualität anästhesiologischer Universitäts-Abteilungen in Deutschland. *Anästhesiol Intensivmed Notfallmed Schmerzther* 1999; **34**: 793–4
7 Boldt J. Forschungsqualität anästhesiologischer Universitäts-Abteilungen in Deutschland. *Anästhesiol Intensivmed Notfallmed Schmerzther* 1999; **34**: 794–5
8 Maleck WH, Boldt J, Wickenhäuser R. Deutschsprachige Publikationen Deutscher Anaesthesiologischer Universitäts-Abteilungen. *Anästhesiol Intensivmed Notfallmed Schmerzther* 2000; **35**: 559–66
9 Boldt J, Haisch G, Maleck WH. Changes in the impact factor of anesthesia/critical care journals within the past 10 years. *Acta Anaesthesiol Scand* 2000; **44**: 842–9

Editor—We thank Dr Maleck for his interest in our work and are pleased to be given the opportunity to reply to his letter. Our analysis produced data on publication productivity and the international recognition of different countries/regions in the field of paediatric anaesthesia during the period from 1993 to 1998.[1] As Dr Maleck pointed out, we showed that the number of publications per German anaesthesiologist was smaller than for anaesthetists in other countries such as the European states or North America.

However, this does not necessarily imply that, as Dr Maleck stated, 'German paediatric anaesthesia in the mid-1990s was far behind its major competitors'.

First, publications in peer reviewed journals listed in Medline™ represent only one of the criteria which acknowledges the standing of 'paediatric anaesthesia' in a given country. Important additional factors such as, for example, reports in periodicals not listed in Medline™, chapters in books, contributions on the World Wide Web,[2] presentations at scientific meetings and—most importantly—the quality of day-to-day clinical practice, have to be taken into account in the appreciation of the international position of this anaesthetic subspecialty. Second, as discussed in our paper, differences in the publication activity of various countries may also be influenced by differences in the respective medical systems (structure of fund-raising, career development, financial support of scientific activity), or on other factors, such as language or training.[3] As mentioned in our paper,[1] a certain publication bias towards Anglo-American authors has been postulated to affect international publication patterns.[4,5]

We are grateful to Dr Maleck for the information that the German anaesthesia journal *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* (*AINS*) did not have an impact factor during the period from 1993–1998, although it was listed in Medline™ at that time. However, the 1999 Science Citation Index lists *AINS* with an impact factor of 0.473[6,7] (total citations=319, immediacy index=0.140, source items=136).[7] The Science Citation Index uses ANASTH INTENSIV NOTF as the current abbreviation for *AINS*[7] (confirmed by the editorial office of the journal). We were misled by the abbreviation ANASTH INTENSIVMED, used in the Science Citation Index[8] for another German anaesthesia journal (*Anästhesiologie & Intensivmedizin*) which, in contrast, is not listed in Medline™ and is therefore not included in our study sample. According to our method, publications in *AINS* should not be included to calculate a country's cumulative impact factor (cIF-country) as they do not have an impact factor. This results in a 15% lower cIF-country for German authors in paediatric anaesthesia (74.58), compared with the one we originally reported in Table 6 (88.38). Similarly, this reduces the mean impact factor (Table 7) of German publications on paediatric anaesthesia, which now stands at 0.738 instead of 0.875. For completeness, the one publication in *AINS* by US authors was subtracted leading to a small reduction in the cIF-country (from 1084.41 to 1083.41) and in the mIF (from 2.122 to 2.092) for US-American authors.

However, these calculations do not affect the ranking of the countries listed in both tables and, as Dr Maleck agrees, the reported results on this aspect of our study remain valid: German authors published less on paediatric anaesthesia during the period studied compared to their colleagues from the USA, UK, Japan, Canada, Scandinavia or France. Additionally, the relative international representation ('visibility'[9]) of the respective articles was lower when the impact factor was used for the calculation of the respective figures. However, as discussed in our paper, the value of the impact factor as a measure of quality remains a matter of controversy.[1,6,10]

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9 Fávaloro EJ. Medical research in New South Wales 1993–1996 assessed by Medline publication capture. *MJA* 1998; **169**: 617–22

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Preventing epidural catheter obstruction

Editor—Most anaesthetists who combine general and epidural anaesthesia will be familiar with the problem of mechanical epidural catheter obstruction.

Rare manufacturing defects in the catheter[1,2] and early blood clot obstruction should be avoidable by careful inspection and by giving the 'test dose' prior to induction. More troublesome in our experience is late obstruction by intra-operative catheter kinking or stretching.[3] We have had several such cases during radical prostatectomy when the surgeon has insisted on steep Trendelenberg repositioning with exaggerated lumbar lordosis. Only then has the catheter obstructed, presumably kinked in a deepening skin fold. The problem is not rectifiable until post-operatively when the chance to optimize intra-operative regional analgesia has been missed.

Our solution to the problem uses a sterile, polyurethane nasogastric feeding tube ('Flowcare', Chatel Medical Devices, Chatel-St-Denis, Switzerland) cut to length. The tube is passed over the extracorporeal portion of the epidural catheter following removal of the epidural needle but prior to attaching the epidural filter. The guarded catheter is then taped to the back along the normal route with a thin layer of gauze padding separating it from the skin.

The stiff nasogastric tube provides a protective envelope for the fine epidural catheter and the gauze keeps the arrangement comfortable. Since using this simple technique, we have had no further problems with intra-operative mechanical catheter obstruction and we would commend the technique to others.

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1 Chandhok D, Vijayakumar E. An unusual case of epidural catheter obstruction. *Anesthesiology* 1999; **91**: 895–6

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British Journal of Anaesthesia 86 (3): 460–3 (2001)

Book Reviews

International Anesthesiology Clinics. Vol. 38: Number 3: 2000. *Airway Management*. W.E. Hurford (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 242; indexed; illustrated. Price US$66. ISBN 00205907.

This issue of International Anesthesiology Clinics is written by staff from hospitals of the Harvard group, principally Massachusetts General Hospital. It deals with airway management in a very broad sense.

In the first chapter, entitled *Techniques of Endotracheal Intubation* the sections on anatomy, preparation for intubation, nasotracheal intubation, and verification of tube placement are clear and well presented. However, the section on laryngoscopy techniques could have been better. Optimization of external laryngeal manipulation *by the laryngoscopist* should have been recommended. The technique described for the straight laryngoscope is not optimal. Many anaesthetists may consider that the optimal position of the laryngoscopist, when the patient is lying on the ground, is not an important issue. However, in the trauma or resuscitation situation, it may make all the difference, and recent work on this subject is reviewed. The dissemination of such practical issues is a major justification for review journals.

The chapter on the role of the laryngeal mask airway (LMA†) in the difficult airway contains much useful information. However, the photograph purporting to show the glottic opening in front of the aperture bars of the LMA is of limited value. The epiglottis is very prominent, but the posterior cartilages are faint and the vocal cords are ghost-like. A clearer photograph would have helped those new to fibreoptic intubation through the LMA. The technique of ILMA use is well illustrated with diagrams from the manufacturer's handbook. However, successful use will be more likely if the reader refers to the important information in the manufacturer's handbook or videotape.

The key section of the chapter on the difficult airway concerns methods of securing the airway. A number of techniques are discussed, but the descriptions are brief, and anyone wishing to attempt these techniques for the first time will need to seek more detail elsewhere. For example, the gum elastic bougie is mentioned, but signs of tracheal placement and the optimal technique of 'railroading' are not described. The summary of this chapter emphasizes the importance of practical, well-thought out contingency plans. In the text, these plans are based on a brief discussion of the ASA guidelines (1993) for management of the difficult airway. Suggested approaches to nine types of airway problems are shown in a table. It is a major deficiency that neither here nor elsewhere in this issue is there any consideration of obstructive laryngeal disease. This omission is serious, as awake intubation is not normally the approach of choice for such patients. Although the central role of the LMA in management of the unexpected difficult intubation is discussed in the previous chapter, it should have been included in this chapter.

The equipment, learning curve, preparation of the patient, and technique of fibreoptic intubation are described well. Although complications are mentioned, recommendation of oxygen insufflation through the fibreoptic laryngoscope may be unwise. Most anaesthetists will rarely have to deal with airway trauma or the burns patient, and will be better prepared if they have read good recent reviews. The chapters on these topics are excellent. The chapter on the parturient is generally satisfactory. However, the suggestion that administration of additional doses of neuromuscular blocker may be needed will not find favour in UK practice. There are good, though brief, reviews of tracheal and tracheostomy tubes, and of percutaneous tracheostomy. The only percutaneous technique described in detail is the 'Blue Rhino' system.

Non-invasive positive pressure ventilation (NPPV) and Heliox therapy are considered in 'Techniques to avoid intubation'. Successful use of NPPV requires great attention to detail, and practical aspects are well considered. Helium is of proven value in management of upper airway problems, including laryngospasm, but its value in small airway disease is more controversial. Asthma is considered to be a disease of large airways, and the use of helium in this and other airway diseases is reviewed. Delivery systems for helium administration are described well.

Finally, the chapter on swallowing disorders after tracheal intubation and tracheostomy covers all aspects of airway protection and laryngeal function. The sections on physiology and the effects of tracheal intubation and tracheostomy should be of interest to all anaesthetists, but the detailed discussion on evaluation and management will principally interest intensivists.

I enjoyed the many historical details in this issue. However, it is not true that William Macewen preferred nasal to oral intubation. He did not use nasal intubation, a technique subsequently introduced by Kuhn. It is also disappointing that credit is not given to Murphy for the first use of fibreoptic intubation.

This issue has weaknesses. There are a fair number of typographical errors, and the quality of writing varies greatly between chapters. It cannot be recommended as an introductory text on airway management, as some of the clinical recommendations are controversial, and many important topics are omitted. However, this issue has great strengths. It deals well with important, but infrequent, clinical situations. Consequently it should be widely read by experienced anaesthetists. Many important recent advances are included, and I have learned much from it.

J. J. Henderson

Practical Intensive Care Medicine. Charlie Corke. Published by Butterworth-Heinemann, Oxford. Pp. 160. Price £18.99. ISBN 0750647523.

I warmed to this unpretentious little book the more I read it. The aim of the book is to give those who are new to the intensive care unit an introduction to practical issues in patient management. There are 16 chapters which cover various topics, from arterial blood gas analysis to haemodynamics, pulmonary artery catheter data and electrolyte interpretation, to name a few. Each chapter presents a series of short clinical problems, and presents pertinent questions, allowing the reader to formulate his or her own opinion before reading the answer. Occasionally there is an interjection from a sceptical medical registrar or confused surgeon, which the reader is asked to sort out. I found this light approach quite appealing to keep the narrative moving and me interested. The problems are relevant and recognizable and I feel sure they arise from the author's own practice.

When data interpretation is not enough, small boxes of 'mini-tutorials' are inserted into the text. For example, permissive hypercapnoea is described in a mini-tutorial of three paragraphs, with references provided. The book is generally up-to-date, with references up to and including 1999. Inevitably, however, some of the answers given are not quite 'up-to-the-minute', and some of

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the concepts slightly old fashioned. The chapter on respiratory problems is the weakest one in the book in this respect, especially when dealing with modes of ventilation. Most intensivists would now focus on pressure-controlled ventilation rather than SIMV and CMV modes as the author does. However, it is the nature of the speciality to change. Landmark papers have been published since the book was printed; most of the fundamentals of practice presented here remain constant. The book suffers the occasional glaring typographical error which hinders some progress through the clinical problems. There are some gaps: there is only tangential reference to metabolic problems, and none to nutrition in the critically ill. As these issues are complex and views are changing, I feel that it is appropriate to include them in an introductory text.

The great joy is that this book deals with genuinely *practical* intensive care. It is clear that the author is a practising intensivist, one who enjoys his job, and enjoys teaching the finer points of his vocation. I have not seen pulmonary artery catheter insertion and data interpretation, or chest drains, for example, described as well in as few words as they were here.

The last chapter deals with 'General Management Issues'. Some of the most important and troublesome problems arising for young doctors first exposed to intensive care revolve around the 'whens' and 'whys' of treatment initiation and treatment limitation. The author has presented several difficult situations for the reader to think about, and gives, as always, sound and sensible advice.

I would recommend this little book to all trainees coming to work in intensive care units for the first time. It will help them through many of the vexing problems they will be faced with in their first weeks—many that their seniors may have forgotten were vexing to them once. In short, this brief introduction into intensive care problems should be welcomed by any neophyte on the unit as an outline of the challenges that lie ahead.

S. J. Harper

The Simpson Handbook of Obstetric Anaesthesia. A.S. Buchan, G.H. Sharwood-Smith. Published by Albamedia for RCS Ed., Electronic booklet; indexed; illustrated.

My knowledge of computers is limited and I was therefore interested in the challenge of reviewing this electronic hand booklet of obstetric anaesthesia. Accessing the booklet on a computer was easy with fool-proof instructions. It is an updated version of the non-electronic form which was published in 1991, with some interesting extras. It comprises of nine chapters which are basic, factually correct, and well compiled. These chapters include information and advice for the labour ward anaesthetist—applied physiology, analgesia for labour, regional and general anaesthesia for operative delivery, and many emergency procedures. Protocols are presented for major haemorrhage, failed intubation, and maternal and neonatal resuscitation. The diagrams, which appear in colour, are clear and pertinent. There are up-to-date references which, if one is internet linked, can be easily examined in abstract form on 'Pubmed'. Again, this function proved simple to master. The appendices present informative lists of information. There is an interesting facility titled 'discussion'. This enables one to E-mail one of the authors with suggestions or enquiries. The authors hope that this will develop the content of the book.

Before reading this booklet, I believed that a hand booklet should be what its name suggests—a book small enough to be held in the hand and thumbed through over a cup of coffee or referred to when faced with a dilemma. This electronic hand booklet is much better. Nowadays, with the need for referenced protocols on labour wards it will be most valuable, enabling one to print off up-to-date protocols. Preparing tutorials will be easier. For trainees, who are almost all adept with computers, it is a more appealing way to present information.

I am glad to have this electronic booklet as an addition to our delivery suite and I congratulate its authors on producing it.

L. T. Fahy

Progress in Pain Research and Management. Vol. 16; *Proceedings of the 9th World Congress on Pain.* Marshall Devor, Michael C. Rowbotham, Zsuzsanna Wiesenfeld-Hallin (editors). Published by IASP Press, Seattle. Pp. 1154; indexed; illustrated. Price US$80. ISBN 0931092310.

This important publication contains the best of the presentations at the triennial World Congress on Pain, the largest and most prestigious of congresses on pain therapy and science. The 105 chapters represent the very best of the lectures, workshops, mini-symposia, or research papers at a large and very successful meeting.

The first section presents the 'house-keeping' aspects of the congress, *Pain, IASP, and the Vienna Congress*, with the addresses of the departing and in-coming presidents. It also contains a very valuable chapter in which Pat Wall discusses the intellectual roots of pain research and therapy, highlighting the plasticity of the central nervous system. He quotes the example of a nociceptive-specific cell in lamina I being converted into a wide-dynamic-range cell by the arrival in its vicinity of a brief volley of impulses in unmyelinated afferents from muscle. He further states, 'At any one moment, the entire structure is in a single state that can change fundamentally as a consequence of neuronal activity and of slowly changing chemistry. This dynamic state needs to be appreciated as such and not oversimplified as a fixed state with rare alternative options.'

New work in the basic sciences is presented first, starting with cellular and molecular mechanisms of the peripheral and central nervous systems. Cloning of receptors and ion channels has focused on gating of channels in sensory neurones by ATP, protons, and capsaicin. These channels may be non-specific cation as well as sodium channels. The discussion about the nociceptive effects of ATP is partly based on the premise that surgical sympathectomy, sympathetic ganglion blocks, and guanethidine blocks are more effective in preventing pain in Complex Regional Pain Syndrome Type I (CRPSI) and sympathetically maintained pain than adrenoceptor antagonists or reserpine (which depletes norepinephrine but not ATP from sympathetic nerve terminals). This sadly does not take into account the clinical evidence now accepted that guanethidine blocks have no efficacy in CRPSI! It is sad that the World Congress appears to have failed in one of its primary aims, to integrate clinical with basic science evidence.

Presentations include topics such as the up regulation/down regulation of specific subtypes of sodium channel genes on dorsal root ganglion neurones following axotomy leading to: an increased number of channels and sodium ion conductance; reduced threshold for generation of action potentials; abnormal expression of sodium ion channels in inflammation; and all are separate to the effect of local prostaglandin and serotonin production on the channels. Activity related regulation is also discussed, as well as further evidence for spontaneous firing of dorsal root ganglion neurones in patients with neuropathic pain.

$A\beta$ touch afferents contribute to central sensitization, and in its presence actively produce tactile allodynia, spontaneous ectopic discharge and ectopic mechanosensitivity of $A\beta$ afferents at sites of nerve injury More and more variants of the μ receptor are being discovered. Neurotrophic factors produce sympathetic-sensory coupling in the skin, and damaged nerve trunks or dorsal root ganglion in inflammation or nerve injury.

The section on *Experimental models of pain: peripheral mechanisms* is introduced by Torebjork's John J. Bonica distinguished lecture, which focused on the various types of C nociceptors. Mechano-responsive units may be involved in detection and localization of very acute noxious events. Mechano-insensitive C nociceptors are less suited for detection and localization of initial noxious events but can become spontaneously active for long periods following chemical irritation or inflammation, which contribute to primary hyperalgesia to heat and tonic pressure. Topical or intradermal capsaicin produces a loss of epidermal nerve fibres with concurrent decrease in heat pain and mechanical (sharp) pain sensation. Tumour necrosis factor (an important mediator of inflammation) applied to animal nerve models produced acute ectopic activity and allodynia. Neurogenic inflammation from intradermal capsaicin produces widespread vasodilatation, which is mediated by spinal mechanisms. Substance P antagonists, effective analgesics in animals and antidepressants in humans, have yet to be shown to be effective in human pain.

Experimental models of pain: central mechanisms presents central substance P receptors and activity, cholecystokinin, and differential spinal release of amino acid neurotransmitters. Animal experiments suggest that better effects can be achieved with TENS if low-threshold high-frequency stimulation is used to produce some analgesia, then switching to high-threshold low-frequency stimulation, which will be better tolerated at higher amplitude. The multiplicity of pain pathways and their plasticity is also presented. Quantitative sensory testing in painful syringomyelia shows two distinct sub-groups of patients, suggesting different patho-physiological mechanisms and therefore the need to consider different therapeutic approaches.

Genes and environment presents work on genetic factors for pain in mice, and in human migraine, especially the P/Q-type calcium channel, and CRPS type I. Pre-operative consumption of soy protein suppressed pain behaviour in rats after partial sciatic ligation.

Four papers are presented in the section on *Imaging pain*. The future benefits of the new imaging techniques are still difficult to evaluate, changes being dependent on attentional aspects as much as pain.

Nociceptive, inflammatory, and sympathetic-related pain presents on visceral hyperalgesia and urogenital pain. One presentation discusses the role of gonadal hormones and their ability to make chronic pain worse. The most illuminating paper, however, was that forearm immobilization in volunteers, without injury, produced transient signs and symptoms of CRPSI. We must now see CRPSI as a response to disuse, and not as a disease entity! Sympathetic-afferent coupling in the dorsal root ganglia after spinal nerve injury may be due to neurogenic vasoconstriction.

There is a salutatory presentation on iatrogenic pain syndromes in the section on neuropathic pain. Spinal root compression is also discussed; with the realization that simple mechanical stimulation of the nerve root is probably not the cause of pain such as sciatica, but direct mechanical stimulation of, or traction on, the dorsal root ganglion. The pathophysiology of repetitive strain injury is also discussed.

The section on pharmacological approaches to pain management starts with the obligatory presentation on evidence-based medicine. Most of this section enlarges current knowledge, leading towards a more rational pharmacological approach. Cyclo-oxygenase inhibitors have been shown to have a central analgesic action. Adenosine, cannabinoids, delivery systems, and opioids for chronic non-malignant pain, are all discussed.

Physical approaches to pain management leads in with an interesting paper which suggests that 2 Hz sub maximal stimulation has no analgesic effect on experimental pain, and can therefore be used as a placebo for studies of TENS treatment. Whether this will be supported in studies on chronic pain will need to be awaited. Predictors for success of spinal cord stimulation are presented, together with its value in severe angina pectoris. A meta-analysis of motor cortex stimulation for chronic neuropathic pain supports its value.

Psychological and cognitive approaches to pain management complete this excellent compendium of presentations. Richard Gracely discusses the non-specific effects of treatment, highlighting the efficacy of sham operations for angina, and surgical exploration alone for trigeminal neuralgia. The value of cognitive-behavioural therapy is reinforced, with the suggestion for its use earlier in the development of the pain, and the importance of low self-efficacy in disability and depression. The impact of the solicitous spouse is also discussed.

Throughout the book is the maxim that acute pain is a warning and should preserve the individual from danger. I continue to be perplexed by this view. The official IASP definition of pain, 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage', should have moved us away from the idea that pain is a warning. It informs of a damaging event, *after* the event, which is too late to avoid that damage! I liken it to having a warning light in the cockpit of an aeroplane that lights up to tell you that you have crashed! Warning systems to be effective need to inform of imminent problems, not problems that have already happened! It is this fear of damage from pain that is so disabling for our chronic pain patients.

This book is the most up-to-date compendium of knowledge on pain in existence, and represents an essential item for any pain clinician's library.

Tim Nash

Clinician's Guide to Pain. 1st edn. T.W.I. Lovel and W.U. Hassan. Published by Arnold (member of the Hodder Headline Group), London. Pp. 191; indexed; illustrated. Price £29.99. ISBN 0340740973.

Written by two authors, this is a book of two parts. The first deals with pain due to cancer whilst the second addresses rheumatic pain. Pain due to other causes is not included.

Both sections of the book start with an explanation of the physiology and anatomy of pain. Although repetitive, the rheumatic section includes a description of the painful joint and is more detailed than the equivalent chapter in the cancer section. It therefore helps the reader gradually to build up knowledge. However, there is a lack of clarity regarding different types of pain fibre and an error in the explanation of the gate control theory of pain, which may cause confusion to any reader not already conversant with the physiology of pain.

Pain due to cancer is covered in the first part of the book. The preface states that the emphasis is on evidence-based medicine and, in many of the chapters in this section, numerous studies are quoted. However, the results are in the main body of the text, which makes them difficult to assimilate; they interrupt the otherwise readable style of this section. References to the author's own clinical practice, comments on historical aspects of analgesia, illustrations and case reports all add interest.

Part two, rheumatic pain, is divided into chapters each dealing with a separate disease process. In addition, the initial chapter outlines some analgesic drugs, their pharmacology, uses and contraindications. This second part is consistently and well laid out, allowing the reader to quickly find the information required. Tables are used for lists of, for example, drugs, symptoms and risk factors (although the red and yellow flag system of risk factors in back pain is not mentioned). Helpfully, drugs and their doses, are stated. Unfortunately, amitriptyeline is consistently referred to as an antidepressant, giving the impression that this is its mechanism of action in pain management, and some statements are not backed up with a reason or evidence, for example 'avoid using opioids'. Non- pharmacological or surgical treatments, such as acupuncture, TENS, psychological and physiotherapy treatment are mentioned but with little detail. It is not always clear which measures should be instituted in the GP surgery and which in a specialist centre.

The final chapter concerns corticosteroid injections. There is good advice on patient information and the types of steroid used. However, the instructions for performing each injection, even with the colour illustrations, are brief with the barest mention of contraindications and potential complications. Some, for example injection into the hip joint or caudal epidural space, must not be attempted using only the explanation in this book. Trying to instruct a beginner on so many injections in seven pages is probably over-ambitious.

This book is probably of interest to family physicians and nurses and therapists in palliative care and rheumatology units, as stated in the preface. It gives an overview of pain in cancer and rheumatic disorders and the possible treatments available. It is not a textbook for those wishing to train in pain management but it may prove useful to those who are developing an interest in palliative care or rheumatic pain, as a source of references for further reading.

H. Romer

The Management of Acute Pain. 2nd edn. G. Park, B. Fulton and S. Senthuran. Published by Oxford University Press, Oxford. Pp. 196; indexed; illustrated; Price £19.95. ISBN 0-19-2624679.

In the preface of the first edition of their book, the authors state that their aim is to provide simple guidance to those who prescribe and administer drugs for acute pain relief, particularly junior medical and nursing staff. In the second edition of this useful and eminently readable book, they undoubtedly continue to achieve their end. The authors acknowledge that since the first edition was published in 1991, the treatment of acute pain has evolved and improved, and the second edition has taken this into account.

The authors of the first edition have widened the scope of the text by recruiting two other doctors and two specialist pain nurses to contribute to the second edition. The new edition has four more chapters than the first, three of which are concerned with epidural and spinal modes of analgesia and the pharmacology of opioid drugs in these anatomical areas (subjects covered by a single chapter in the first edition). One of the medical contributors, Anne Coleman from Hexham, has written a new chapter entitled *The acute pain service*. This provides the reader with a comprehensive insight into the undoubted benefits of such a service, together with some of its pitfalls.

There are several more illustrations and tables accompanying the text compared with the first edition, but despite being 40 pages longer, the book remains concise and easily readable as it guides the reader through the anatomy, physiology, pharmacology, and treatment of acute pain. There are excellent chapters on everything from simple pharmacological management and the principles of local anaesthesia, to complex regional blockade techniques and the use of antiemetics, a sometimes neglected subject in books about acute pain. Yet again, there is a practical chapter discussing the management of seven well thought out pain case studies which cover a wide range of problems including pain in children and burns.

Although too short at 196 pages to go into the broader complexities of pain (an admission that the authors make at the beginning of the book), and not intended to replace existing comprehensive texts, there is a thorough list of references on a chapter by chapter basis at the end of the book for the interested reader. It is a convenient size and will fit just as easily into a doctor's white coat pocket as the departmental or ward bookshelf. At £19.95, it will certainly not overstretch even the tightest of budgets.

The successful treatment of pain must be a goal that we all aspire to in our day-to-day life as medical practitioners, and as a final year trainee in anaesthesia, I would have no hesitation in recommending this little gem to both trainee doctors and nurses as an aid to such aspirations.

W. E. Bickerstaffe

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

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Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

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Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

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the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia,
the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

EDITORIALS

287 Lidocaine Neurotoxicity in the Obstetric Patient: Is the Water Safe?

CARDIOVASCULAR ANESTHESIA
(Society of Cardiovascular Anesthesiologists)

291 Diastolic Dysfunction and Cardiac Surgery
299 Ethanol and Stunned Myocardium
306 Pulmonary Blood Flow and PETCO$_2$
314 PentaLyte® Resuscitation, Heparinoids, and Thrombotic Mediators
320 Nitric Oxide and Coagulation
324 Diaspirin Cross-Linked Hemoglobin and Vascular Tone
329 Hematocrit, Hypothermia, and Neurological Outcome
335 Cerebral Embolism in Aortic Stent-Grafts (Case Report)
338 Imaging a Differential Perfusion Cannula (Technical Communication)
341 Fat Elimination from Autologous Blood (Technical Communication)
344 Heparin-Induced Thrombocytopenia and Lepirudin (Case Report)

AMBULATORY ANESTHESIA
(Society for Ambulatory Anesthesia)

347 Home Postoperative Analgesia: Comparison of Tramadol, Metamizol, and Paracetamol
352 Esmolol vs Remifentanil During Desflurane Anesthesia

PEDIATRIC ANESTHESIA
(Society for Pediatric Anesthesia)

358 Bilateral Vocal Cord Palsy in a Child (Case Report)

ANESTHETIC PHARMACOLOGY
(International Society for Anaesthetic Pharmacology)

362 Xenon and c-Fos Expression in Ketamine
369 Remifentanil Heat Pain Threshold

TECHNOLOGY, COMPUTING, AND SIMULATION
(Society for Technology in Anesthesia)

375 Efficacy of Esophageal Detector Devices
379 Factors Influencing Hurricane® Delivery
384 Electrocautery and Monitoring Devices
389 Proton-Transfer-Reaction Mass Spectrometry Online Air Quality Monitoring

ECONOMICS AND HEALTH SYSTEMS RESEARCH

393 Patients' Willingness to Pay for Antiemetic

OBSTETRIC ANESTHESIA

401 Lidocaine-Induced Transient Neurologic Symptoms Postcesarean Delivery
405 Transient Neurologic Symptoms
410 Levobupivacaine Sparing by Fentanyl

NEUROSURGICAL ANESTHESIA

415 Continuous Positive Airway Pressure and Cerebral Blood Flow
418 Ischemic Tolerance and the Spinal Cord
424 Anesthesia for Stereotactic Frame Placement

CRITICAL CARE AND TRAUMA

428 Adhesion Molecules and Transforming Growth Factor-β1 in Ventilator-Induced Lung Injury
437 Sepsis, Neutrophils, and IV Anesthetics
442 Gram Stain of Mini-Bronchoalveolar Lavage Fluid

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

448 Dextromethorphan for Pain Relief After Knee Surgery
455 Continuous vs Patient-Controlled Analgesia Femoral Nerve Sheath Block
460 Sciatic Nerve Block and Leg Rotation
463 Effect of Epidural Block on Lymphocyte Subsets
470 Plasma Lidocaine Concentration During Surgery
476 Glucocorticoid Inhibition of Hyperalgesia
483 Effect of Percutaneous Neuromodulation Therapy Montage on Analgesic Response
488 Carbamazepine and Morphine in Neuropathic Pain
496 Bupivacaine Enantiomers on Ca^{2+} Channels
502 Microfabricated Microneedles (Brief Communication)
505 Use of Electroanalgesia for Pain Management (Medical Intelligence)
514 Thoracic Epidural Anesthesia for Bilateral Reduction Mammoplasty in a Patient with Klippel-Feil Syndrome (Case Report)

GENERAL ARTICLES

517 A Simple Algorithm for Tracheal Intubation
523 Intubation with Different Anesthetics
529 Sameridine and Ventilators
535 Shaker and Halothane in Fruit Flies
542 Carbon Monoxide During Anesthesia
548 Auricular Acupuncture: State Anxiety
554 Difficult Airway and Coffin-Siris Syndrome (Case Report)

LETTERS TO THE EDITOR

BOOK AND MULTIMEDIA REVIEWS

IARS PRECONVENTION ISSUE

SEE INFORMATION INSIDE

ISSN 0003-2999 Volume 92, Number 2, February 2001
www.anesthesia-analgesia.org

BJA
International Journal of Anaesthesia
Volume 86 Number 4 April 2001

EDITORIALS

465 I. KISS and indices of pulmonary oxygen transfer
C. E. W. Hahn
467 II. Continuous cardiac output by pulse contour analysis?
J. J. van Lieshout and K. H. Wesseling
469 III. Lessons from Stafford
J. R. Sneyd
473 IV. Local anaesthesia for eye surgery—no room for complacency
G. S. Thind and A. P. Rubin

CLINICAL INVESTIGATIONS

477 Effect of changes in arterial-mixed venous oxygen content difference ($C(a-\bar{v})_{O_2}$) on indices of pulmonary oxygen transfer in a model ARDS lung
M. Nirmalan, T. Willard, M. O. Columb and P. Nightingale
486 Estimation of changes in cardiac output from the arterial blood pressure waveform in the upper limb
N. W. F. Linton and R. A. F. Linton
497 Transoesophageal echocardiography in cardiac and vascular surgery: implications and observer variability
D. Schmidlin, D. Bettex, E. Bernard, R. Germann, M. Tornic, R. Jenni and E. R. Schmid
506 Intercurrent drug therapy and perioperative cardiovascular mortality in elective and urgent/emergency surgical patients
J. W. Sear, S. J. Howell, Y. M. Sear, D. Yeates, M. Goldacre and P. Foex
513 The auditory evoked response as an awareness monitor during anaesthesia
E. Loveman, J. C. Van Hooff and D. C. Smith
519 Ocular microtremor: a tool for measuring depth of anaesthesia?
S. Bojanic, T. Simpson and C. Bolger
523 Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia
C. Lysakowski, L. Dumont, M. Pellégrini, F. Clergue and E. Tassonyi
528 Antinociceptive properties of neurosteroids IV: pilot study demonstrating the analgesic effects of alphadolone administered orally to humans
C. S. Goodchild, A. Robinson and R. Nadeson
535 Persistent back pain after spinal anaesthesia in the non-obstetric setting: incidence and predisposing factors
K. Schwabe and H.-B. Hopf

LABORATORY INVESTIGATIONS

540 Cytochrome P4502B6 and 2C9 do not metabolize midazolam: kinetic analysis and inhibition study with monoclonal antibodies
N. Hamaoka, Y. Oda, I. Hase and A. Asada
545 Naloxone improves functional recovery of myocardial stunning in conscious dogs through its action on the central nervous system
T. P. Weber, J. Stypmann, A. Meißner, M. Große Hartlage, H. Van Aken and N. Rolf
550 Effects of sevoflurane on dopamine, glutamate and aspartate release in an *in vitro* model of cerebral ischaemia
C. C. Toner, K. Connelly, R. Whelpton, S. Bains, A. T. Michael-Titus, D. P. McLaughlin and J. A. Stamford

REVIEW ARTICLE

555 Neurofibromatosis: clinical presentations and anaesthetic implications
N. P. Hirsch, A. Murphy and J. J. Radcliffe

SHORT COMMUNICATIONS

565 Intrapartum epidural catheter migration: a comparative study of three dressing applications
S. M. Burns, C. M. Cowan, P. M. Barclay and R. G. Wilkes
567 Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine
D. J. A. Vaughan, N. Ahmad, N. K. Lillywhite, N. Lewis, D. Thomas and P. N. Robinson
570 Small-dose selective spinal anaesthesia for short-duration outpatient gynaecological laparoscopy: recovery characteristics compared with propofol anaesthesia
A. V. G. Stewart, H. Vaghadia, L. Collins and G. W. E. Mitchell
572 Analgesic efficacy of tramadol 2 mg kg^{-1} for paediatric day-case adenoidectomy
H. Viitanen and P. Annila
575 Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass
D. Royston and S. von Kier
578 Circulating tetrahydrobiopterin concentrations in patients with septic shock
H. F. Galley, A. E. Le Cras, K. Yassen, I. S. Grant and N. R. Webster

CASE REPORTS

581 Review of management of purpura fulminans and two case reports
J. Nolan and R. Sinclair
586 Intra-operative and post-operative hypercapnia leading to delayed respiratory failure associated with transanal endoscopic microsurgery under general anaesthesia
K. Kerr and G. H. Mills
589 Acute respiratory and metabolic acidosis induced by excessive muscle contraction during spinal evoked stimulation
Y. Tohdoh, S. Sumita, T. Kawamata, K. Omote, S. Kawana and A. Namiki

594 CORRESPONDENCE

603 BOOK REVIEWS

605 ERRATA

CONTROVERSIES AND DEVELOPMENTS IN INTENSIVE CARE

A Combined Meeting of
Liverpool University Dept. of Anaesthesia,
The Mersey School of Anaesthesia and Perioperative Medicine
& The Association of Merseyside Intensive Care Units

Friday May 11th 2001 - Liverpool Maritime Museum

Morning Sessions: *Presentations:*

Session 1:

a) **Is ECMO the answer to the problems of acute lung failure?**
Speaker: Mr. Richard Firmin, Consultant Cardiac Surgeon, Leicester

b) **New issues in the management of patients with respiratory failure – How to avoid ECMO**
Speaker: Prof. Nigel Webster, Aberdeen University

Session 2:

c) **New methods of measuring Cardiac Output. Are any likely to be of use?**
Speaker: Dr. Gernot Marx, Senior Lecturer in Anaesthesia and Intensive Care, Liverpool.

d) **Blood Transfusion on the ITU.**
Speaker: Dr. Gary Masterson, Consultant in Anaesthesia and Intensive Care,
Royal Liverpool University Hospital, Liverpool

Afternoon Session: *Debates:*

Chairman: Prof. M. Leuwer

1) **Limited resource dictates that ITU admission should be limited to those likely to survive.**
For: Dr. Kathy Rowan, Director of ICNARC, London
Against: Dr. Julian Bion, Reader in Intensive Care Medicine, Birmingham

Chairman: Prof. J. Hunter

2) **PA Catheters are an under used ITU resource.**
For: Dr. Mark Bellamy, St. James's University Hospital, Leeds
Against: Dr. Mervyn Singer, Bloomsbury Institute of ICU medicine, London

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Meeting Friday 11 May 2001 Application Form (Please print)

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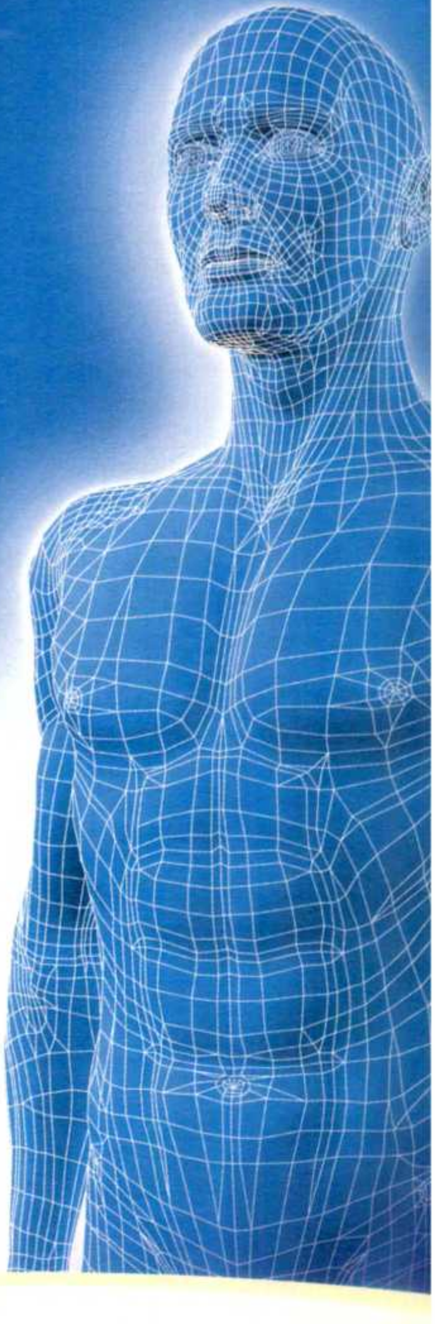

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Innovation in Critical and Community Care

Editorial Notices

European Academy of Anaesthesiology Award Programme

1. EAA Clinical Scholar Research Award

This award is created to further the understanding of anaesthesiology and related sciences of clinical practice through clinical investigations. Research must involve human subjects. The maximum amount to be awarded for any project is 25 000 Euro. Please note that institutional indirect expenses are not funded.

To qualify, the principal applicant must be a member of the European Academy of Anaesthesiology (EAA) and be an investigator with a research record who has yet to establish a history of substantial funding. The award will go to a research project, which is judged by peer review to have high scientific merit and high probability of success. Priority funding will be awarded to proposals which are independent of other grant support. Experienced investigators working in new areas will receive consideration. The proposed project must have direct relevance to the speciality of anaesthesiology. Applicants must submit their curriculum vitae as well as an outline of their proposed research project. Furthermore, the application should be accompanied by a letter from the chairman of the department outlining the applicant's research qualities.

2. EAA Teaching Recognition Award

The purpose of this award is to discover an individual with outstanding teaching skills besides his/her research skills. The award winner will be required to give a total of five lectures. One lecture must be presented at the annual EAA congress. The other four lectures will be given in each of four different European countries, either at university departments or at the annual congress of the national societies. The award winner will receive a travel reimbursement for every lecture up to 1250 Euro. The remaining travel expenses will be paid by the host departments or congress organizers, if necessary. The maximum amount to be awarded is 5000 Euro.

Applicants should not be older than 45 years and should have finished their PhD or an equivalent degree. To qualify, applicants must be a member of the EAA. Applicants must submit their curriculum vitae as well as an outline of their lecture. Each application must be accompanied by a letter from the applicant's chairman, and two letters from residents in their own department, outlining the applicant's teaching qualities.

3. EAA Training Award

This award is created for young anaesthetists, including residents in their last year of training, with the aim of completing their training in another European department of anaesthesiology, recognized as a European centre for training of anaesthesiologists. The winner of the award will receive 2000 Euro per month for a maximum of six months.

To qualify, the applicant must have passed at least the Part I of the European Diploma of Anaesthesiology or be a member of the EAA. Candidates must submit a curriculum vitae as well as a description of the special training which they intend to follow. Furthermore, each application must be accompanied by a letter from his/her chairman as well as a letter from the chairman of the host department.

Please submit one original application and six copies to the EAA Secretary, **before April 30, 2001.** Prof. Dr. Th. Pasch, Universitats Spital Zürich, Direktor des Institut für Anästhesiologie, Rämistraße 100, CH-8091 Zürich, Switzerland.

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, March 23, May 4, July 6, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

Neuroanaesthesia Society of Great Britain and Ireland

Churchill College, Cambridge, UK, March 29–April 1, 2001

The Neuro Update Course takes place on March 29–30, 2001. The NAS meeting 2001 takes place March 31–April 1, 2001

For further information on the meeting please visit our website: www.nas.dundee.ac.uk or contact: Conference Secretary (NAS 2001), Department of Anaesthesia, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. Tel: +44 1223 217897; Fax: +44 1223 217223; E-mail: christine.butler@msexc.addenbrookes.anglox.nhs.uk

Advances in Objective Assessment of Hand/ Upper Extremity Function and Outcome

Genval (Brussels), Belgium, April 20–21, 2001

For further information please contact: F. Schuind, MD,

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PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail:fschuind@ulb.ac.be

Final FRCA Revision Course

Leicester Royal Infirmary, Leicester, UK, May 1–4, 2001

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice. Course director: Dr Paul Sharpe.

Fees: £290 Non-residential (including lunch and refreshments); £390 Residential at local hotel (including lunch and refreshments).

For a booking form please contact Christine Gethins, Tel: 0116 258 5291 (places strictly limited).

Combined Scientific Meeting (CSM 2001) of The Australian and New Zealand College of Anaesthetists (Faculty of Intensive Care and Faculty of Pain Medicine) and The Hong Kong College of Anaesthesiologists

Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

Developments and Controversies in Intensive Care—a one day symposium

Maritime Museum, Liverpool, UK, May 11, 2001

Organized by the University Department of Anaesthesia in conjunction with the Mersey School of Anaesthesia and the Association of Merseyside Intensive Care Units.

For further information, please contact: Joyce Coleman, Tel: 0151 293 2202 or Sue Costigan, Tel: 0151 293 2396

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail:akabogu@mcn-nuernberg.de; www: http://www.mcn-nuernberg.de

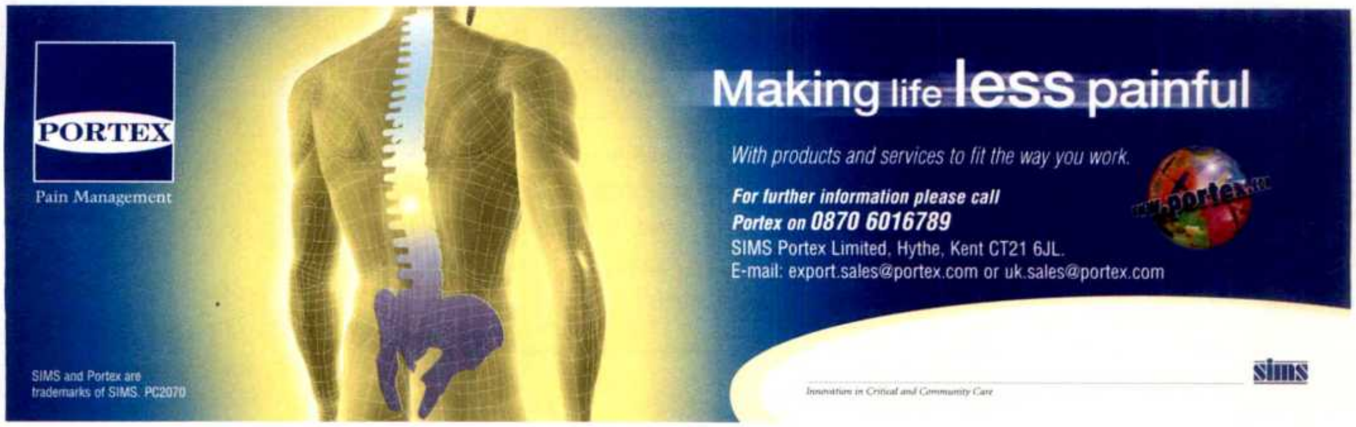
Annual Symposium Dental Sedation Teachers Group

Sedation in the 21st Century

The Village Hotel and Leisure Club, Cardiff, UK, Tuesday May 22, 2001

The group provides a forum for all individuals who are interested in the teaching of conscious sedation in dentistry. The membership includes dental and medical practitioners from university, hospital, community and general practice backgrounds. The programme is designed to allow an interchange of views on the use of conscious sedation in dentistry. For further details please visit our website: www.dstg.co.uk

Speakers: Dr P. Averley, Dr G. Lahud, PDS Initiative Billingham; Dr C. Bell, Dept of Oral Surgery, Bristol Dental School; Dr I. Cooper, Department of Health; Dr D. Craig, Associate Specialist, GKT; Dr A. Neilson, Associate Specialist, Dundee Dental School; Dr D. Vaughan, Senior Dental Officer, MPhil student, Cardiff; Dr M. Wilson, Senior



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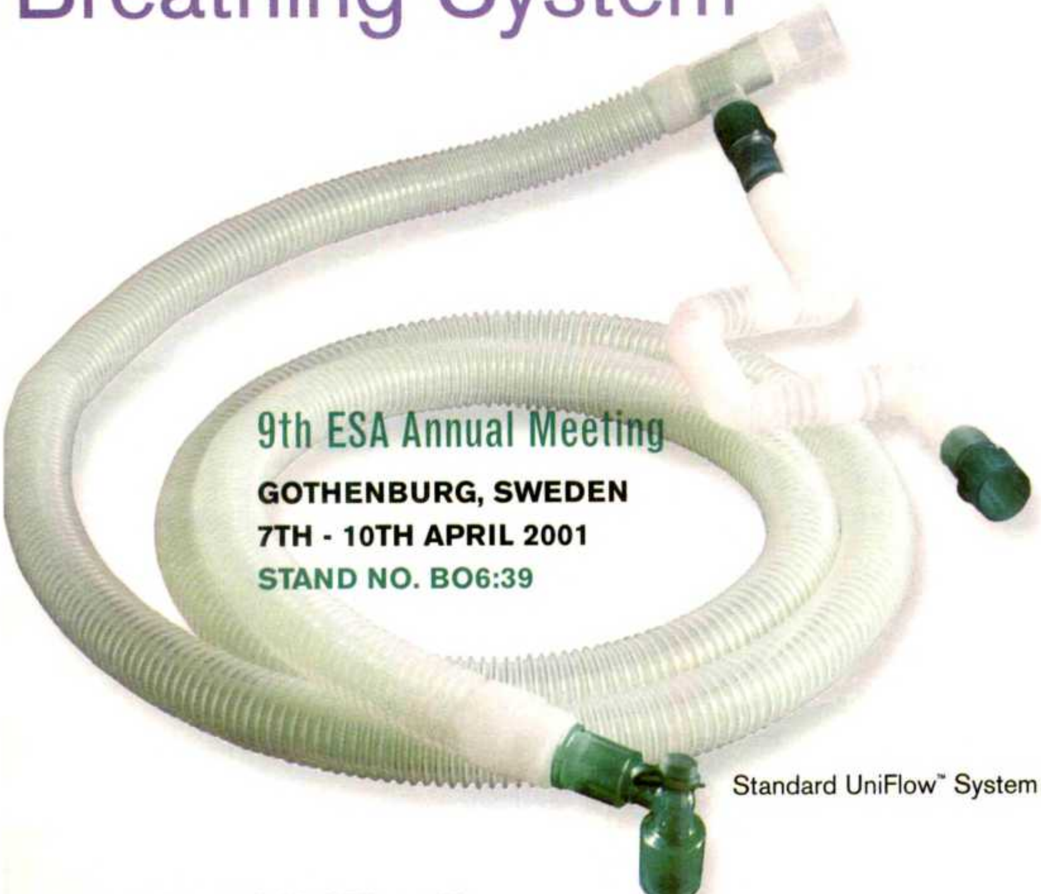

9th ESA Annual Meeting

GOTHENBURG, SWEDEN
7TH - 10TH APRIL 2001
STAND NO. BO6:39

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Lecturer in Restorative Dentistry, Manchester; C. Pennell, E. Williams, A. Millard-Davis, Cardiff Sedation Nurses.

Organiser: Dr N. D. Robb, Sedation Suite, UWCM Dental School, Heath Park, Cardiff CF14 4XY, UK. E-mail: robbnd-@cardiff.ac.uk

Symposium Venue: Village Hotel and Leisure Centre, 29 Pendwyallt Road, Coryton, Cardiff CF14 7EF, UK. Tel: 02920524300; Fax: 02920524313; E-mail: village.car@cybase.co.uk; Website: www.vhl.co.uk

Accommodation: Contact hotel and mention DSTG. Rate £75 B&B including use of leisure facilities.

Registration: Members £55 Non-members £65. Annual symposia are open to members and non-members. Attending non-members will be offered one year's membership of the group included in the registration fee.

Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, UK, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
Tel: 01442 879000. Fax: 01442 870999.

E-mail: enquiries@prestige-promotions.co.uk

5th International Conference on Memory, Awareness and Consciousness: Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, NY, June 1–3, 2001

For further information, please contact: (for scientific enquiries) Ruth Reinsel, PhD, Department of Anesthesiology and Critical Care, Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6038; Fax: +1 212 772 8646; E-mail: mac@mskcc.org; website: www.maacc.org or (for other enquiries) Office of Continuing Medical Education, Box 31, Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6754; Fax: +1 212 717 3140; E-mail: cmeinfo@mskcc.org; website: www. mskcc.org

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92; E-mail: SSAI.20-01@rito.no
Web site: www.ssai2001.org

7th International Neuromuscular Meeting

Belfast, UK, June 21–24, 2001

For further information, please view the website http://www.nisca.org/nmb2001/ or contact Professor R. K. Mirakhur, Department of Anaesthetics and Intensive Care Medicine, The Queen's University of Belfast, Whitla medical Building, 97 Lisburn Road, Belfast BT9 7BL, Tel: 44 (0) 28 9033 5785; Fax: 44 (0) 28 9032 9605; E-mail: r.mirakbur@-qub.ac.uk.

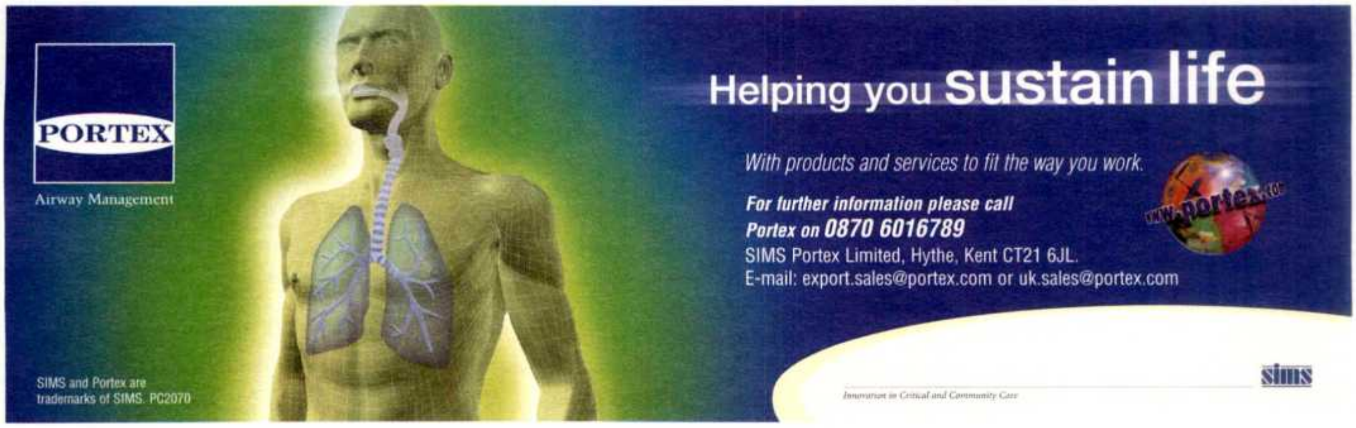
Abstracts are invited for presentation at the meeting. Please visit the website for instructions.

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts



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of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Ventilation Through the Ages

ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

International ventilation conference covering all aspects of respiratory support from neonates through to adulthood.

To be placed on the list for registration details, please contact: Sue Hubbard, ERMEC, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK. Tel +44 (0)1482 674007; Fax: +44 (0)1482 586587; E-mail: suehermec@hotmail.com

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: +91 812 670 7575 Ex. 138, E-mail: skghaste@yahoo.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: **(Deadline – November 1, 2001)** Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY

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International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia 19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

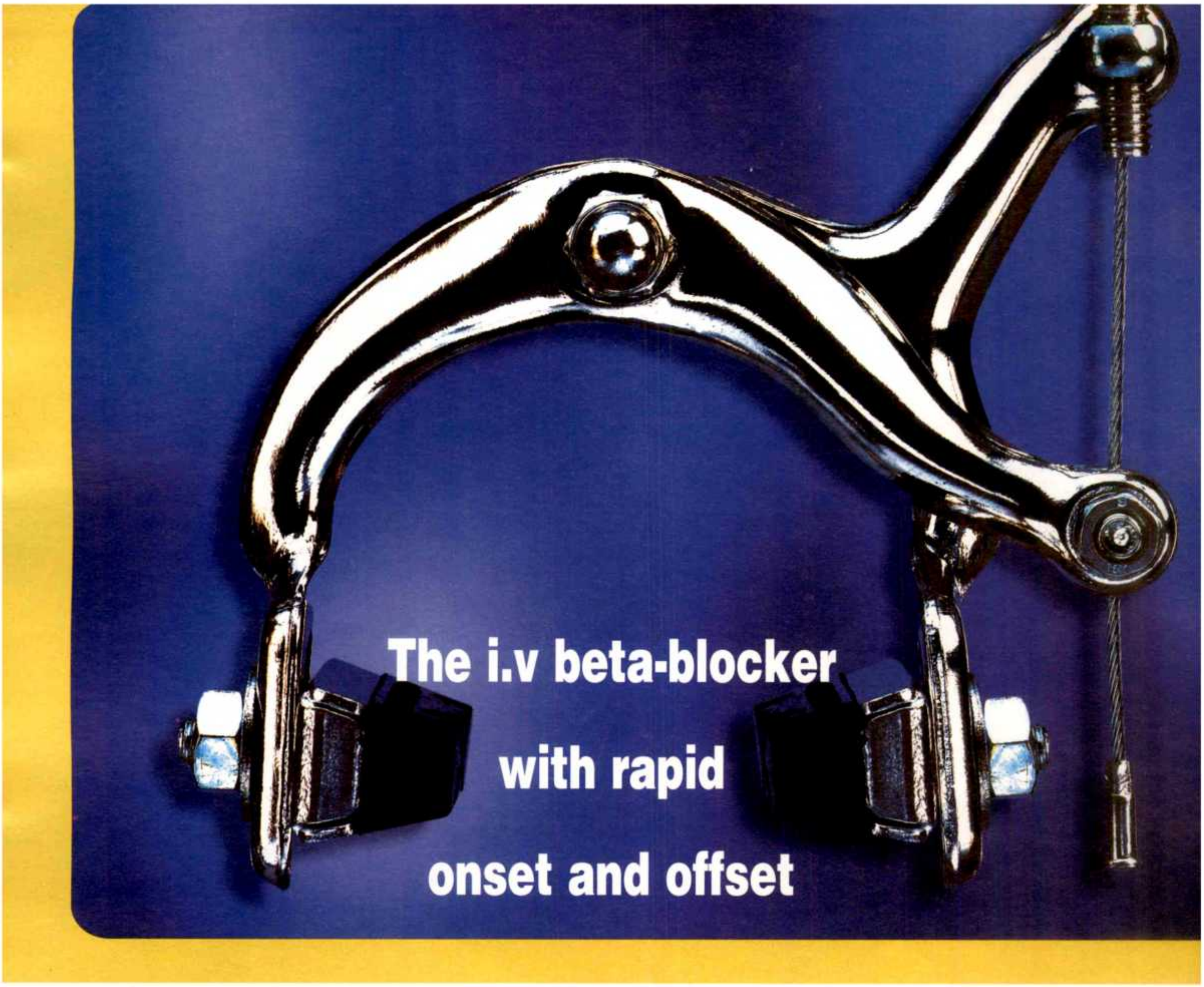
E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com



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IBLOC ® (esmolol HCl)
CRIBING INFORMATION

e refer to the data sheet before prescribing. **Presentation** ules containing 2.5g esmolol hydrochloride in 10ml sterile aqueous ntrated solution (250mg/ml) to be diluted before intravenous stration. Vials containing 100mg esmolol hydrochloride in 10ml aqueous solution (10mg/ml) for intravenous administration without n. **Uses** For the short-term treatment of tachycardia and ension occurring in the perioperative period and supraventricular rrhythmias including atrial fibrillation, atrial flutter and sinus ardia. **Dosage and administration** BREVIBLOC 2.5g ENTRATE MUST BE DILUTED BEFORE INFUSION with an riate intravenous fluid to give a final concentration of 10mg/ml and d into a large vein. Brevibloc 100mg is a ready-to-use preparation oncentration of 10mg/ml. The following dose regimens may be a. For intraoperative treatment - during anaesthesia when iate control is required, give an 80mg loading bolus over 15-30 ds followed by a 150 micrograms/kg/min infusion. Titrate the n rate as required up to 300 micrograms/kg/min. b. Upon ning from anaesthesia - administer an infusion of 500 grams/kg/min for four minutes followed by a 300 grams/kg/min infusion. c. For post-operative situations - when time for titration is available give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. d. For supraventricular tachyarrhythmias - give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150 and 200 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. **Contra-indications, warnings, etc.** *Contra-indications* Brevibloc is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock and overt heart failure. There is no experience with Brevibloc in pregnancy and, although animal tests have shown no teratogenic effect, the use of Brevibloc in women where pregnancy is suspected or confirmed should be avoided. *Warnings and precautions* Use with caution in patients with bronchospastic disease or impaired renal function or diabetes. Brevibloc should also be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities and Brevibloc should not be administered within 48 hours of discontinuing verapamil. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Brevibloc. The dosage of either agent may be modified as needed to maintain the desired haemodynamics. Infusion concentrations of 20mg/ml have been associated with significant venous irritation and thrombophlebitis in animals and man. Extravasation of 20mg/ml may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10mg/ml or infusion into small veins or through a butterfly catheter should be avoided. *Use in Children* The safety and effectiveness of Brevibloc in children have not been established. *Use in Elderly* Analysis of data from 252 patients over 65 years of age indicated no variations in pharmacodynamic effects; however no special studies in the elderly have been conducted. **Adverse effects** Most frequently observed side effect has been hypotension. Other reported side effects have included bradycardia and bronchospasm. **Pharmaceutical precautions** BREVIBLOC 2.5g CONCENTRATE MUST BE DILUTED BEFORE USE. BREVIBLOC IS NOT COMPATIBLE WITH SODIUM BICARBONATE. **Legal category** Prescription Only Medicine. **Basic NHS. price** Brevibloc 2.5g 10ml Concentrate Ampoule £65.90; Brevibloc 100mg/10 ml Vial pack of 5 £29.50. **Productlicenceholder and number** Baxter Healthcare Limited, Caxton Way, Thetford, Norfolk, IP24 3SE. Brevibloc 2.5g Concentrate - PL 0116/0318; PA 167/99/2. Brevibloc 100mg/10ml Vial - PL 0116/0319; PA 167/99/1. **Date of Preparation** July 1998 ® Denotes registered trademark

axter
) Baxter Healthcare Ltd

Baxter Healthcare Ltd
Wallingford Road
Compton, Nr Newbury
Berkshire, RG20 7QW.

TRUE ONCE-DAILY

VIOXX® ▼

(rofecoxib)

Selective. Strong. Simple.

VIOXX® ▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib. VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded. *Elderly:* Exercise care when increasing the dose from 12.5 mg to 25 mg. *Hepatic insufficiency:* In mild hepatic insufficiency, do not exceed 12.5 mg once-daily. *Children:* Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs.
Third trimester of pregnancy and lactation. Inflammatory bow
Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pr
significantly impaired renal function, uncompensated hea
or cirrhosis. Use caution when initiating treatment in pati
considerable dehydration. Rehydrate patients prior to
therapy with rofecoxib. Consider the possibility of fluid rete
exercise caution when rofecoxib is used in patients with pr
oedema, a history of heart failure, left ventricular dysfu
hypertension. Maintain appropriate supervision when tr
elderly or patients with renal, hepatic or cardiac dysfunc
rofecoxib. In clinical studies, some osteoarthritis (OA) patie
with rofecoxib developed perforations, ulcers or bleeds
Patients with a prior history of a PUB and patients great
years of age appeared to be at a higher risk for a PUB. At d
higher than 25 mg, the risks of gastro-intestinal symptom
or hypertension are increased. Elevations of ALT and/or
times the upper limit of normal) have been reported in appr
1% of patients in clinical trials with rofecoxib. Any pa
symptoms and/or signs suggesting liver dysfunction, or in
abnormal liver function test has occurred, should be eva
persistently abnormal liver function tests. If persistently abn
function tests (three times the upper limit of normal) are
discontinue rofecoxib. Rofecoxib may mask fever. Use of
is not recommended in women attempting to conceive. *In*

02-02 VOX.00.GB.65590.Jc

VIOXX®

Now with added VIGOR*

Landmark study supports superior GI safety profile compared with conventional NSAIDs

50% reduction in perforations, ulcers and bleeds (PUBs) compared with naproxen (95% CI 0.3-0.6; p=0.001)

*VIGOR – **VI**OXX **G**astro-intestinal **O**utcomes **R**esearch – a landmark study involving 8,076 rheumatoid arthritis patients monitored for GI events[1]. VIOXX is not licensed for rheumatoid arthritis. Patients were randomised to either VIOXX 50 mg once daily, or naproxen 500 mg twice daily for an average of nine months.

Rarely, patients may develop perforations, ulcers and bleeds with VIOXX, but the risk is lower in patients treated with VIOXX than in patients treated with conventional NSAIDs.

'VIOXX' IS LICENSED FOR OSTEOARTHRITIS ONLY, AT A DOSE OF 12.5 mg OR 25 mg ONCE DAILY

lynamic): Warfarin: closely monitor the prothrombin time
herapy with rofecoxib is initiated or changed in patients
arfarin or similar agents, particularly in the first few days.
'ors: administration of 25 mg daily of rofecoxib with
10 mg to 40 mg daily for four weeks to patients with
n was associated with a small attenuation of the
isive effect compared to the ACE inhibitor alone. This
nsidered in patients taking rofecoxib concomitantly with
tors. *Beta-blockers and diuretics:* concomitant use of
ay reduce the antihypertensive efficacy of beta-blockers
and the other effects of diuretics. *Aspirin:* at steady state,
) mg once-daily had no effect on the anti-platelet activity
e (81 mg once-daily) aspirin. Avoid concomitant
on of rofecoxib with higher doses of aspirin or other
'yclosporin/tacrolimus: monitor renal function when
d either cyclosporin or tacrolimus is used in combination.
(pharmacokinetic): Lithium: NSAIDS may increase
ium concentrations. *Methotrexate:* consider adequate
for methotrexate-related toxicity when rofecoxib and
e are administered concomitantly. *CYP1A2 substrates:*
: with concomitant administration of rofecoxib with drugs
etabolised by CYP1A2 (e.g. theophylline, amitriptyline,
ileuton). *Midazolam:* a modest 30% reduction of the AUC
m was seen with rofecoxib 25 mg daily, most likely due
first pass metabolism through induction of intestinal
tivity by rofecoxib. *CYP3A4 substrates:* in spite of a
:tion of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25-mg dose when rofecoxib is used with potent inducers of hepatic metabolism. Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *Pregnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus. *Lactation:* contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure and jaundice.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers:

Tablet 12.5 mg: PL 0025/0383; Tablet 25 mg: PL 0025/0384. Oral Suspension 12.5 mg/5 ml: PL 0025/0385; Oral Suspension 25 mg/5 ml: PL 0025/0386.

Marketing Authorisation holder: Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** February 2001

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Whitehouse Station, NJ, USA.

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References:

1. Bombardier C, Laine L, Reicin A et al. Comparison of upper gastro-intestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528.

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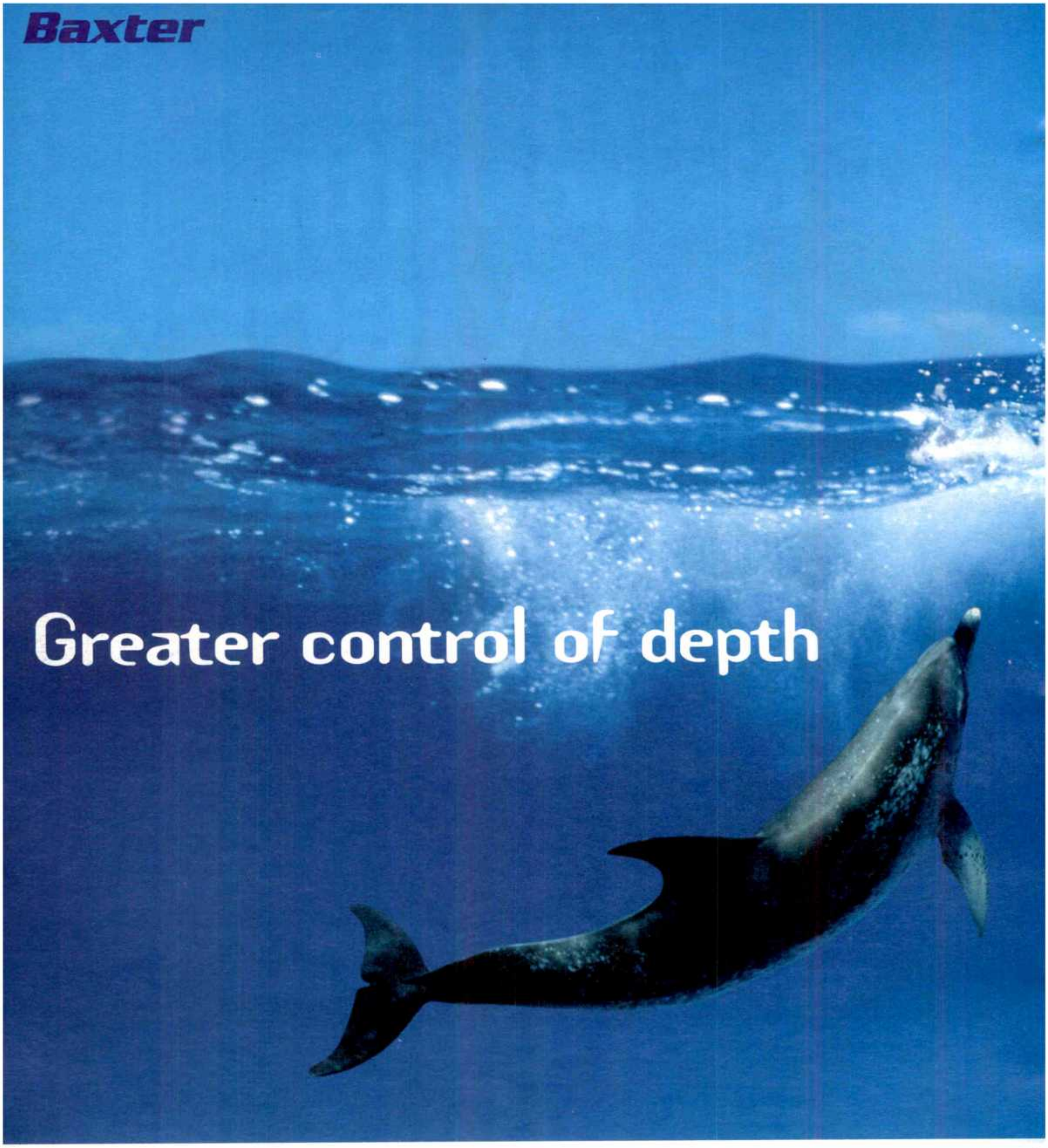
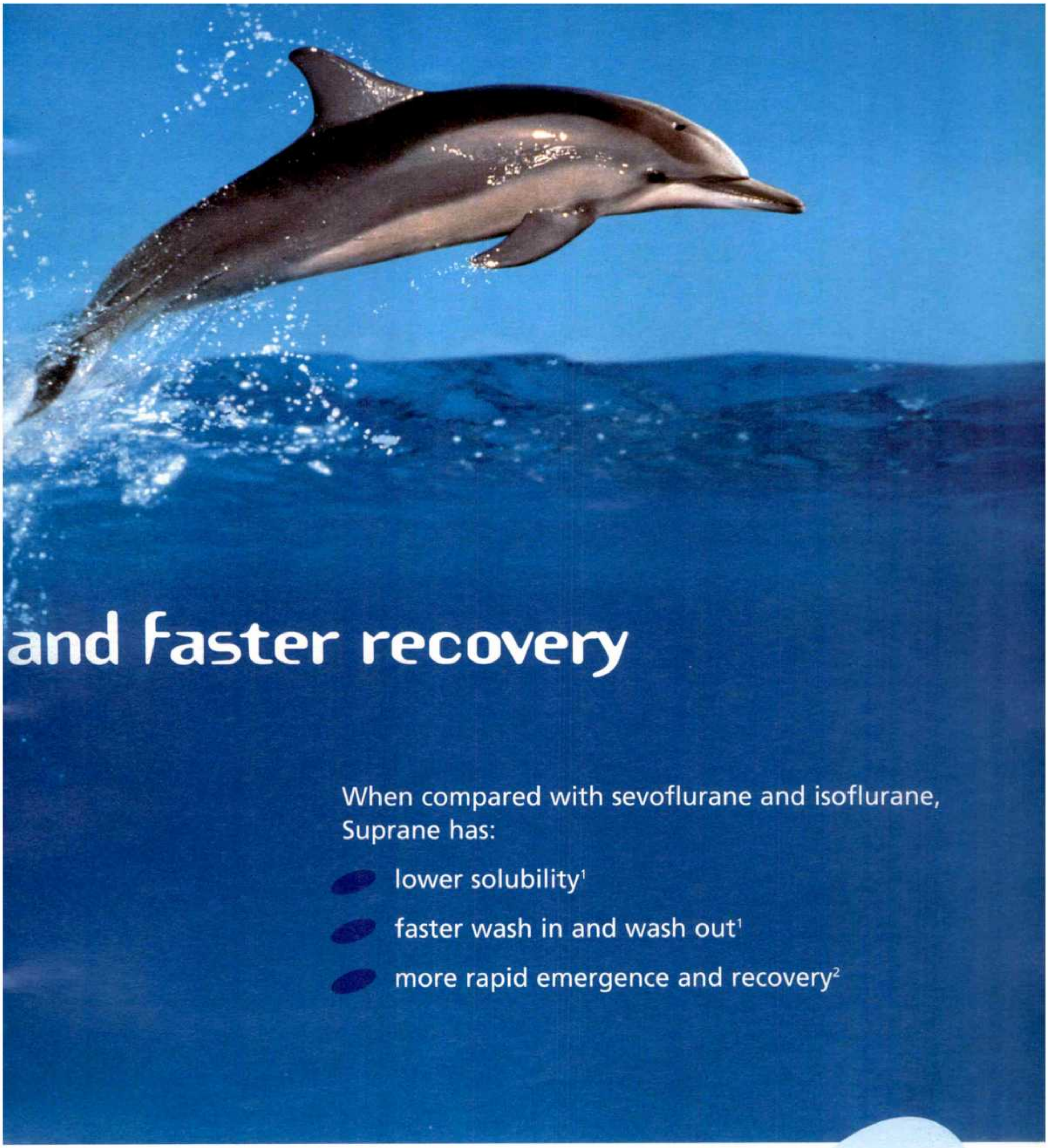


SUPRANE® (desflurane) PRESCRIBING INFORMATION **Presentation:** Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction*. Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance*. Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used fo induction in patients at risk of coronary artery disease or wher increases in heart rate or blood pressure are undesirable **Precautions:** Suprane is not recommended for paediatri induction, or for use in neurosurgical patients. Suprane ma increase CSF or intracranial pressure in patients with spac occupying lesions. A lower concentration is recommended fo hypovolaemic, hypotensive and debilitated patients. Sensitivit hepatitis may be caused in patients previously sensitised b exposure to other halogenated anaesthetics. Suprane ha been shown to trigger malignant hyperthermia. To minimis the risk of formation of carbon monoxide in rebreathin circuits, carbon dioxide absorbents should not be allowed t dry out. Suprane is not indicated during pregnancy or breas


and faster recovery
When compared with sevoflurane and isoflurane, Suprane has:
lower solubility[1]
faster wash in and wash out[1]
more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in maintenance anaesthesia

SUP021/UK/0200

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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EPREX® (epoetin alfa) Increases Preoperative Haemoglobin Levels[1,2]

EPREX Maintains Higher Postoperative Haemoglobin Levels[1,2]

Higher Haemoglobin Results In

Reduction in transfusions[1,2]
Improved early postoperative vigour[3]
Earlier participation in rehabilitation[3]

EPREX Is Generally Well Tolerated

*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

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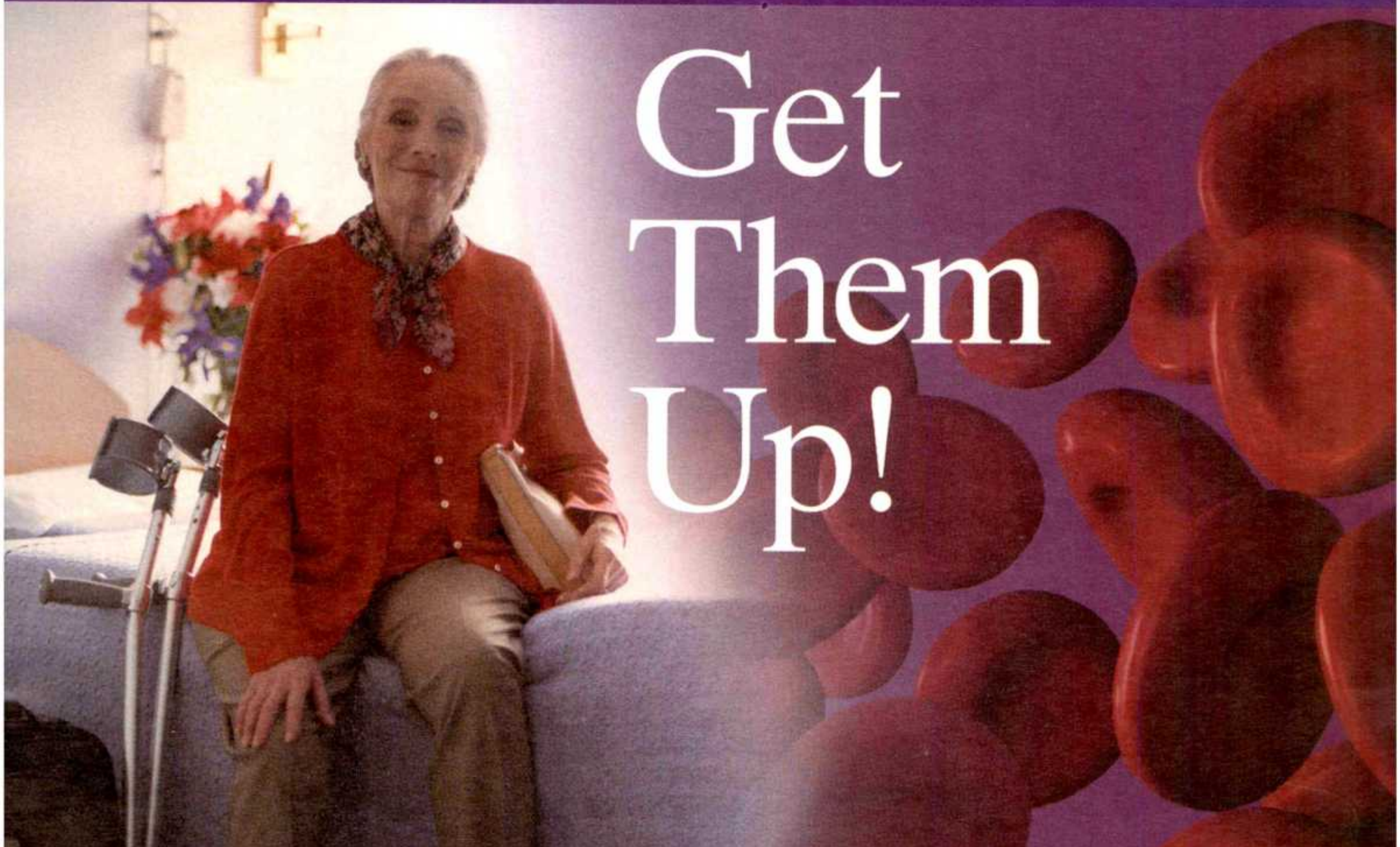

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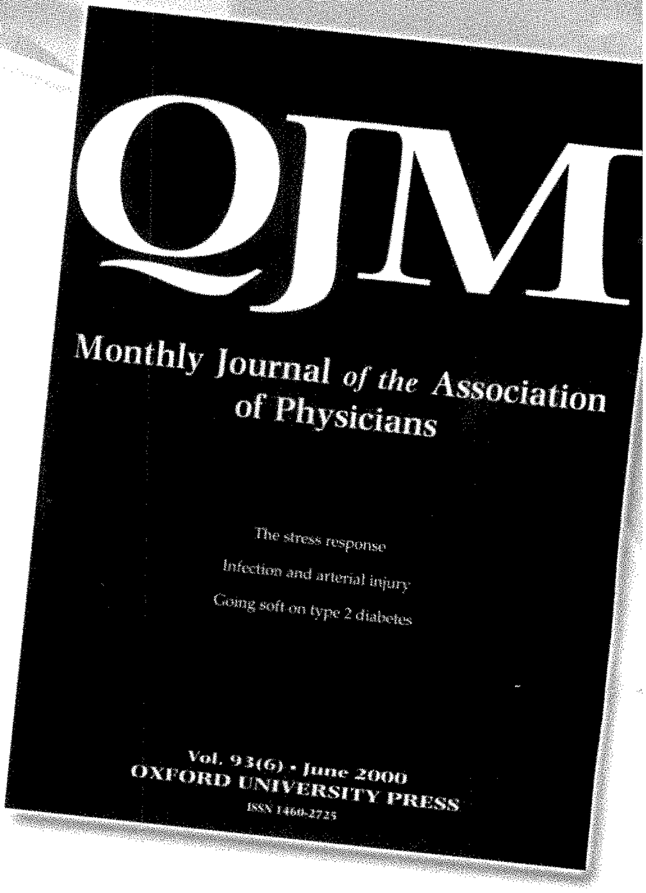

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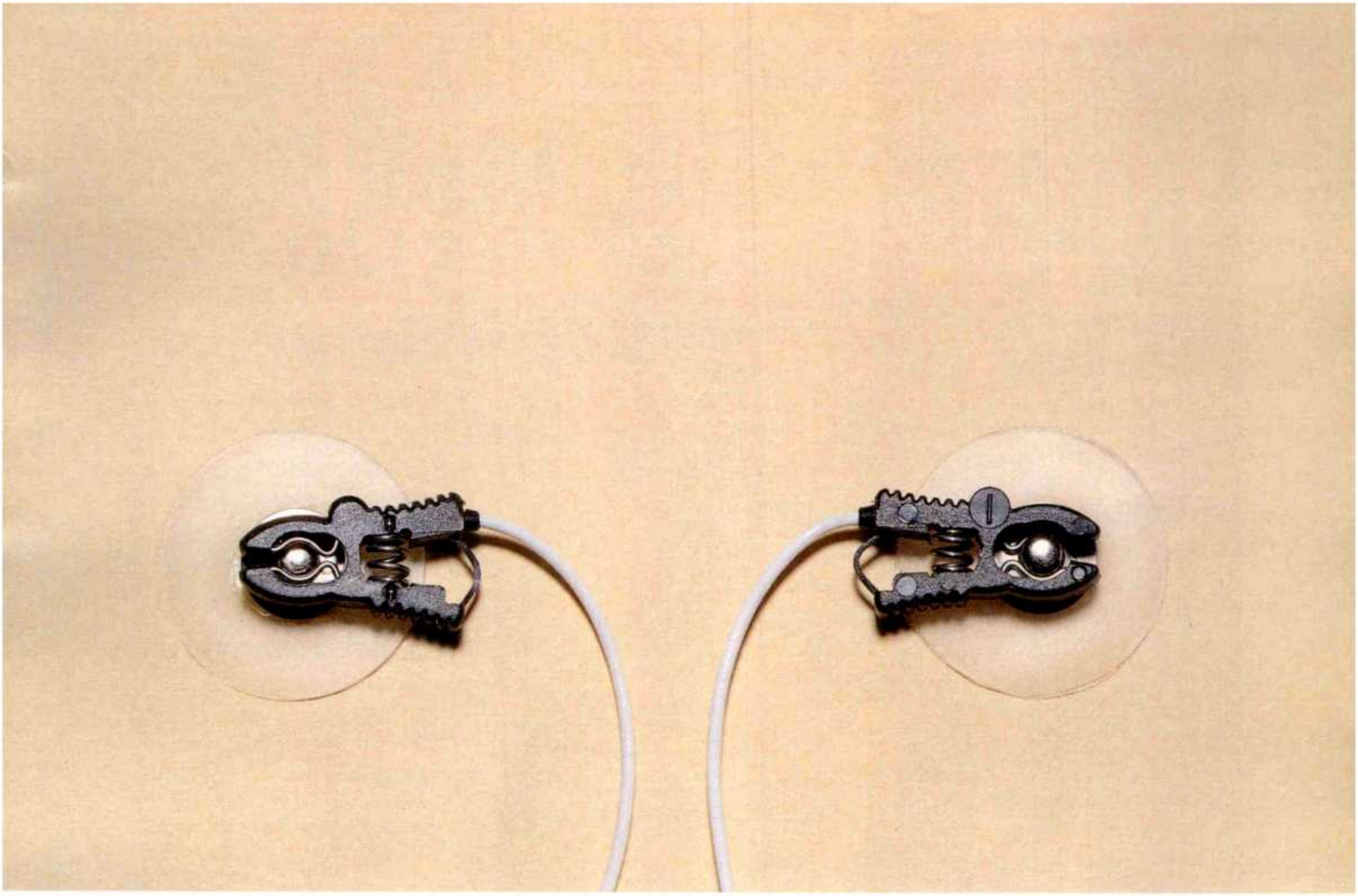

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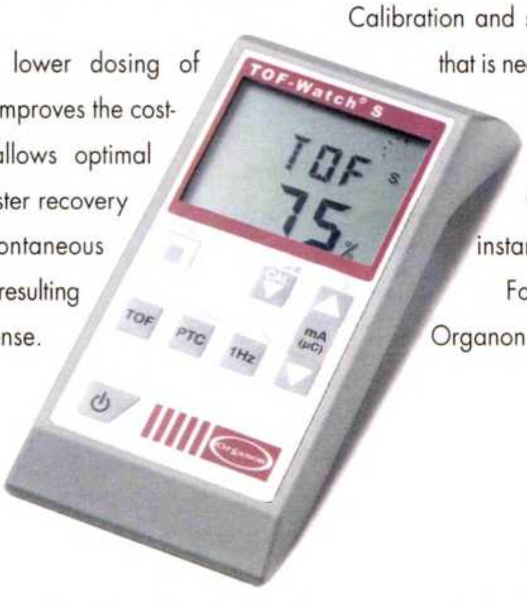

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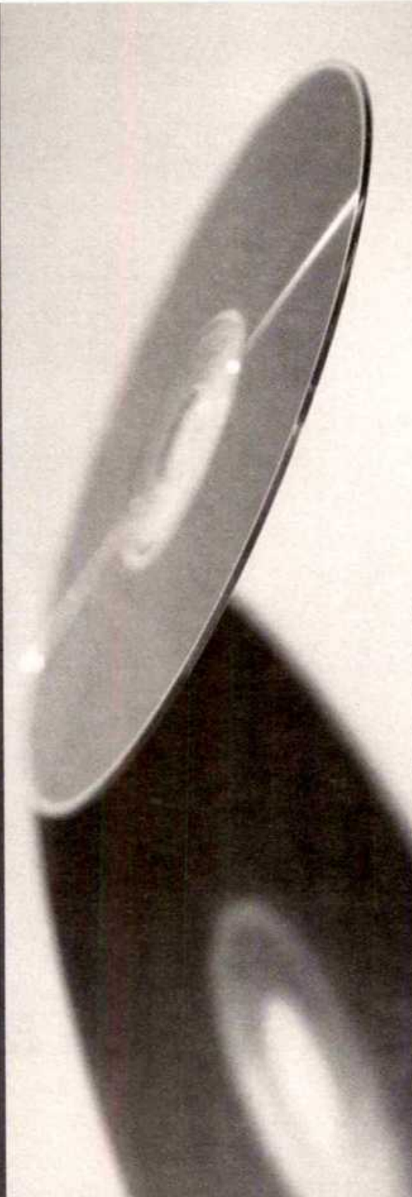

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BJA

"I would have everie man write what he knowes and no more."—Montaigne

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Editorial I

KISS and indices of pulmonary oxygen transfer

KISS, the well-known acronym for 'keep it simple, stupid', is often taken to be good advice for life in general. Not always, though, because simplicity can be very alluring but wrong. A recent editorial[1] on septic shock (a complex, not simple subject), in another journal, had the title 'For every complex problem, there is a solution that is simple ... and wrong'. This writer wishes that he had thought of that clever one-liner.

Suspicion of simplicity could also apply to the whole subject-matter of developing mathematical models and clinically useful indices to describe pulmonary oxygen transfer in the lung. This particular subject has exercised the minds of clinicians and physiologists for decades and forms an essential chapter in textbooks on respiratory physiology, anaesthesia and intensive care medicine. Moreover, for the trainee there is a galaxy of advice, opinions and controversies to be digested.[2–7] The experts offer differing advice. The Holy Grail has always seemed to be a simple index that will quantify the degree of pulmonary oxygen transfer occurring in a given patient, and which can then be used to chart the progress of the patient as lung function improves or deteriorates.

The problem of reconciling theory and clinical practice in blood-gas exchange has long been recognized. A group of (mainly European) specialists from various medical fields was brought together a decade ago to bridge this gap between theory and practice and to discuss and argue about the oxygen status of arterial blood. The proceedings were published as a book, *The Oxygen Status of Arterial Blood* in 1991.[8] A cursory glance at it reveals the real difficulties and complexities involved not only in the measurement of blood oxygen status and the subsequent clinical, therapeutic and diagnostic application of this knowledge, but also in the terminology used to define this status. Over 50 definitions are contained within the appendix! More recently, Siggaard-Andersen and Gothgen[9] considered more than 40 different quantities involved in the complete pH and blood-gas analysis of arterial and mixed venous blood. Out of these they selected 16, including patient temperature, and proceeded to discuss the relevance of these various quantities in clinical practice. Arterial oxygen tension ($Pa_{\mathrm{O_2}}$), of course, figured prominently in their thinking. Hypoxaemia was suggested to be 'synonymous with a decreased $Pa_{\mathrm{O_2}}$' and arterial haemoglobin oxygen saturation was described as 'primarily an indirect measure of $Pa_{\mathrm{O_2}}$'. Thus $Pa_{\mathrm{O_2}}$, not oxygen saturation, was their benchmark.

Correspondingly, because both $Pa_{\mathrm{O_2}}$ and the patient's inspired oxygen concentration, $F\mathrm{I}_{\mathrm{O_2}}$, can be easily measured and, moreover, $F\mathrm{I}_{\mathrm{O_2}}$ varies at will, it is temptingly simple to relate the lung's pulmonary oxygen 'output signal' (the $Pa_{\mathrm{O_2}}$) to its 'input signal' (the $F\mathrm{I}_{\mathrm{O_2}}$) and then compare them. Consequently, these oxygen output and input values have been arranged by many workers to devise indices of hypoxaemia, such as the alveolar–arterial oxygen tension difference, $P(\mathrm{A{-}a})_{\mathrm{O_2}}$; the arterial/alveolar ratio, $P\mathrm{A}_{\mathrm{O_2}}/Pa_{\mathrm{O_2}}$; the respiratory index, $P(\mathrm{A{-}a})_{\mathrm{O_2}}/Pa_{\mathrm{O_2}}$; and the $Pa_{\mathrm{O_2}}/F\mathrm{I}_{\mathrm{O_2}}$ ratio.[5] Each of these indices relates the arterial oxygen tension to the driving force for oxygen transfer in the lung, expressed either as the $F\mathrm{I}_{\mathrm{O_2}}$ or the alveolar oxygen tension, $P\mathrm{A}_{\mathrm{O_2}}$.

The other index of pulmonary oxygen transfer insufficiency, commonly referred to as physiological shunt, pulmonary shunt, right-to-left shunt ($Q\mathrm{S}/Q\mathrm{T}$), or venous admixture ($Q\mathrm{VA}/Q\mathrm{T}$),[10] is based on measurements of the oxygen content of alveolar air, arterial and mixed venous blood. This is described by the well-known shunt[10] or Berggren[11] equation, although the actual contents are often calculated from algorithms incorporated into blood-gas analysers rather than measured directly.

Siggaard-Andersen and Gothgen compared physiological shunt to the indices mentioned above, and concluded that physiological shunt was a better indicator of pulmonary function than any of the oxygen tension indices based on $Pa_{\mathrm{O_2}}$ and $F\mathrm{I}_{\mathrm{O_2}}$.[9] Perhaps it has always been naïve to expect such simple linear indices to describe adequately a system in which the non-linearity of the oxyhaemoglobin dissociation curve is fundamental.

In this issue of the BJA, Nirmalan and colleagues[12] have revisited the subject of pulmonary oxygen transfer indices and have come to the same conclusion as Siggaard-Andersen and Gothgen, but from a different approach. They have taken a published ventilation–distribution (V/Q) curve describing an acute respiratory distress syndrome (ARDS) patient, and have checked its predictions against arterial blood obtained from real patients and then used this model to test three of the indices of pulmonary oxygen

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transfer (namely, $Q\mathrm{S}/Q\mathrm{T}$, $P(\mathrm{A{-}a})_{\mathrm{O}_2}$ and $Pa_{\mathrm{O}_2}/F\mathrm{I}_{\mathrm{O}_2}$) together with the alveolar–arterial oxygen content difference, when $F\mathrm{I}_{\mathrm{O}_2}$ was varied between 0.21 and 1.0. As they admit, various other assumptions had to be made for the sake of simplicity, in order to test the effects of changes in the arterial–mixed venous content difference on their model predictions. Thus, they are by necessity caught in the vortex of applying more simplifications to already simple mathematical models of pulmonary oxygen transfer in the dysfunctioning lung.

The conclusion of the studies of Nirmalan and colleagues is that the popularity of indices based on oxygen tension can be traced to their simplicity and not to their validity. They conclude that $Q\mathrm{S}/Q\mathrm{T}$ is the best available measure of pulmonary oxygen transfer. They suggest that the $Pa_{\mathrm{O}_2}/F\mathrm{I}_{\mathrm{O}_2}$ index, in particular, has gained widespread acceptance for clinical and research purposes because of its simplicity alone. Their bottom line is that there is still no reliable substitute for QS/QT and that 'the inclusion of $Pa_{\mathrm{O}_2}/F\mathrm{I}_{\mathrm{O}_2}$ in the American European Consensus Conference recommendations without qualification may lead to its inappropriate use'.[12]

This is, no doubt, a reasonable conclusion based on the evidence currently available and on the aetiology of the models themselves. Perhaps this is where the problem really lies. In our rush towards simplicity, have we not fallen into the all-too-common trap of equating simplicity with truth? Is it not time to acknowledge that, just as septic shock and the multiple organ dysfunction syndrome are complex,[1 13] so oxygen transfer in the lung, especially in the sick lung, is extremely complex and cannot be described adequately by simple models. The respiratory system is itself amazingly complex, with as many as 23 generations in the respiratory tree, terminating with at least 10^8 alveoli, and breathing is also a dynamic process. Yet we continue to view the human lung as a continuous ventilation process in the steady state. We simply alter $F\mathrm{I}_{\mathrm{O}_2}$ to produce yet another steady state. A cursory glance at a textbook of comparative physiology[14] will reveal that our models of pulmonary oxygen transfer are based on the fish gill model of gas exchange.[15] John Nunn[10] and John West[16 17] developed this model to great effect in their classic teaching books on human respiratory physiology and gas exchange. We certainly owe these two authors an immense debt of gratitude for the clarity of their teaching and for the simple mathematical models they devised and handed down to generations of physiologists and clinicians.

However, this editorial writer has an uneasy feeling that we have remained static in our thoughts and ideas for far too long and have not followed the example of some of our physician colleagues, who have realized for a long time now that disease is a dynamic process. Their models of dynamic disease may be mathematically complex, but if the development of a disease process is complex, then so must be the mathematical model. One illustration of this approach is the book *Dynamic Disease: Mathematical Analysis of Human Ilness*,[18] which gives diverse examples such as non-linear modelling of the immune response, phase-space analysis of dynamic parathyroid hormone secretion, the dynamic structure of tremor in tardive dyskinesia, phase-locking and other non-linear dynamic phenomena in slow insulin and glucose oscillations, self-organizing dynamics in the brain, among others.

Compared with this, our own approach to gas exchange, based on 1960s models, looks very dated now. On the positive side, Hlastala and Robertson, in their recent book *Complexity in Structure and Function of the Lung*,[19] are perhaps pushing us into the 21st century and are persuading us that new models need to be devised whenever the old paradigms fail in clinical practice.

So where do we go to from here? Nirmalan and colleagues have joined a growing group of authors who have challenged the use of clinical indices of pulmonary oxygen transfer that are attractive solely because of their mathematical simplicity. Although they advocate the use of $Q\mathrm{S}/Q\mathrm{T}$, this index is not without its own problems and has, itself, been shown to vary with $F\mathrm{I}_{\mathrm{O}_2}$, sometimes upwards, sometimes downwards and sometimes not at all (the so-called isoshunt phenomenon).[3 10] We also need to remember that the shunt equation is itself built upon the premises of steady-state alveolar gas and continuous blood flow.[10] Others have questioned recently whether the concept of a steady-state pulmonary shunt is adequate to describe the ARDS lung.[20]

Thus, it is not easy at the moment to answer the question 'Where do we go from here?' There are no realistic, comprehensive but still clinically useful mathematical models available. Surely what we need to do is to follow the example of the physicians and to develop realistic dynamic models of gas exchange in the failing lung, even if such models may not provide simple analytical formulae that can be derived and quoted in a textbook? The availability of powerful modern desktop computers and associated software and the growing interest of mathematicians in clinical medicine will surely produce new models of gas exchange that can be used in clinical practice. The advent of the Human Physiome Project[21] (with a concurrent, and necessary, resurgence in systems physiology), with the aim of mathematically modelling all the body's major organs during this new century, will eventually provide accurate models for the anaesthetist and the intensivist. The Human Physiome Project is, however, in its infancy at the moment and the announcement of a comprehensive mathematical model of the pulmonary system is still on the distant horizon.

So, in the meantime, we are left with the classical steady-state and 'continuous blood and gas flow' indices with which we currently work. Some efforts are now being made to introduce tidal ventilation relationships into gas exchange models.[22 23] But even these are based on the balloon-on-a-straw description of the respiratory system, and this is hardly an accurate description of the lung! Still, this model might be better that the fish gill model of pulmonary gas exchange that we work with at present.[15] It is now time for the new generation of anaesthetists not only to challenge the current status quo, as Nirmalan and colleagues have done in this issue,[12] but also to devise new and better mathematical relationships to describe pulmonary oxygen transfer in the ARDS patient. The challenge is there. Who will take it up?

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Editorial II

Continuous cardiac output by pulse contour analysis?

Theoretically, tissue flow should be maintained at the lowest possible arterial perfusion pressure to minimize afterload and myocardial energy expenditure.[1] In the monitoring and measurement of cardiovascular parameters in critically ill patients, however, cardiac output plays a subservient role to arterial blood pressure. Since blood pressure is the principal cardiovascular parameter monitored by the body via baroreceptors, this seems physiological. Furthermore, continuous cardiac output has proved extremely difficult to monitor.

Intermittent methods such as indicator dilution are widely used, but for monitoring purposes cardiac output should be available continuously, like arterial pressure.[2] The paper by Linton and Linton in this issue[3] offers a solution to the monitoring problem by deriving cardiac output from arterial pressure via a cascade of chained models. Such so-called 'pulse contour methods' attempt to determine cardiac stroke volume from characteristics of the arterial pressure pulse. With a first publication in 1904,[4] pulse contour preceded Korotkoff's auscultation paper by 1 year. Both ideas were embraced almost immediately, yet clinical acceptance of the pulse contour and auscultatory methods has differed. Why? Because pulse contour methods are based on solid physical principles and less solid physiological models and they involve substantial computations, all factors that do not ease clinical acceptance.

Major concerns about pulse contour analysis

Non-linearity

If it was possible to know the degree to which the aorta complies to a 1 mm Hg pressure increment and to measure its reponse, then the stroke volume ejected into the aorta could be computed by measuring the associated increase in pressure.[4] For instance, if this compliance was 2 ml per 1 mm Hg pressure increment, then a pressure rise of 40 mm Hg would correspond to a stroke volume of 40×2=80 ml.

The aorta's compliance at low distending pressure is substantial but at higher pressures compliance progressively decreases, resisting overstretching of the aortic wall. Such 'non-linear' behaviour effectively prevents any simple approach to pulse contour estimates of stroke volume.

Typically, for a 50-yr-old patient, aortic compliance might be 3, 1.1 and 0.5 at distending pressures of 50, 100 and 150 mm Hg, respectively. Thus the same 40 mm Hg pulse pressure equates to stroke volumes of 120, 44 and 20 ml, depending on pressure. These values also change with the patient's age; non-linearity is more pronounced in the elderly.

The significance of aortic non-linearity in relation to pulse contour measurement was appreciated as early as 1928,[5] and that of age dependency in 1954,[6] but these two factors were only measured with great precision in 1984.[7] To our knowledge, the variables have been taken into account fully when measuring aortic flow by the Modelflow method only.[8]

Radial artery pressure

The pressure that determines stroke volume is proximal aortic pressure, which is not routinely available. More peripherally recorded pressure waves can be substituted if they bear a known, fixed, and wide bandwidth relationship to aortic pressure. This is almost the case for arterial pressures measured at sites along the arteries in the arm (see references cited by Linton and Linton[3]). The usable physiological bandwidth is a—more than adequate—15 Hz, even to the finger, but a strong resonance is present which must be carefully compensated for by an antiresonance.[9]

Damped waveforms

Intra-arterial pressure is measured predominantly with catheter-transducer systems. With continuous flush devices these systems have become very reliable. Nevertheless, in view of the exposure to blood which this technique produces, a non-invasive method that monitors the quality of the recorded pressure pulse[10] is much needed; it should also signal at an early stage the presence of inadequate recordings.[3] Non-invasive measurement of finger arterial pressure has no significant instrumental damping. Its innovative use with the Modelflow method in an ICU environment has been investigated recently.[11 12]

Inadequate pulse detection

To measure stroke volume, each individual heart beat must be identified in the continuous pressure tracing. Digital computer programs can be designed that hardly ever miss or create a beat, even in the presence of severe arrhythmias or damped pressure curves or when recorded peripherally, such as in the radial artery. Yet, such algorithms are not always implemented.[13]

Absolute cardiac output

The dependence of the properties of the aorta on age, gender, distending pressure and arteriosclerosis are now understood in great detail, but still we are left with aortic diameter at maximal pressure as the single parameter that may vary up to ±40% from the population average.[7 11] The effect is that absolute levels of cardiac output cannot be determined with certainty, although changes in cardiac output can be tracked with precision. These problems have been recognized since 1904. Böger and Wezler[14] were the first to propose a once-only calibration of pulse contour cardiac output by another method such as indicator dilution. It was recently shown[15] that this calibration method may be applicable even after 48 h of monitoring in ICU patients.

Minor concerns

Aortic pathology

A patent aortic valve is required to prevent any back flow that is not modelled. In addition, aortic aneurysms modify the properties of the aorta in unpredictable ways. Changes with sympathetic outflow in smooth muscle tone in the aortic wall may also modify these properties. The amount of aortic smooth muscle, however, is small and major effects have not been reported.

Body position

The properties of the aorta change with distending pressure and so depend on the patient's posture. Yet, between the supine and erect positions, offsets in young adult subjects appear small.[16] Obese patients may show differences in pulse contour-estimated cardiac output due to abdominal compression when moved from the supine to the prone position, however.

Conclusion

Since the major concerns about continuous measurement of cardiac output now have solutions, methods that include these solutions will probably prove reliable and sufficiently precise in tracking changes in cardiac output in critically ill patients. Linton and Linton[3] go a long way in this direction, but early reports cannot be fully accepted before well controlled[17] clinical studies have established the facts in context. Fully non-invasive cardiac output monitoring from arterial pressure could at last be in sight.

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[†] **Declaration of Interest**: Both authors have helped develop and have published on the Modelflow method (mentioned in reference 8). The second author holds a patent on that method.

Editorial III

Lessons from Stafford

In the early 1990s, Professor David Southall supervised paediatric research studies at North Staffordshire Hospital. Following complaints and allegations by the parents of the participating children, a review was set-up and its findings have been published.[1] The process of the review and the fairness of its report have been criticized[2 3] and defended.[3] This editorial addresses the findings of the review and their implications for clinical research in anaesthesia.

The research

The CNEP study

A novel system for ventilation of neonates was evaluated in a randomized controlled trial against standard intensive therapy. The CNEP Ventilator applied a continuous negative extrathoracic pressure as an alternative to tracheal intubation. A report of the study, published in 1996,

Table 1 Principles of the Nuremberg Code.[10] Key principles in obtaining informed consent for research

Consent must be voluntary

The patient:
- must have legal capacity to give consent
- be able to exercise free power of choice
- experience no force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion
- have sufficient knowledge and comprehension . . . to make an understanding and enlightened decision

The explanation must include:
- nature of the experiment
- its duration
- its purpose
- the method and means by which it is to be conducted
- all inconveniences and hazards reasonably to be expected
- the effects upon his health or person which may possibly come from his participation in the experiment

The duty and responsibility for ascertaining the quality of the consent:
- rests upon each individual who initiates, directs, or engages in the experiment
- is a personal duty
- is a responsibility which may not be delegated to another with impunity.

concluded that CNEP reduced the requirement for tracheal intubation and decreased the duration of oxygen therapy required. However, it was associated with increased mortality, cranial ultrasound abnormalities and pneumothoraces (although these increases were not statistically significant).[4]

The hypoxia study

This investigation simulated the effects of air travel by administering 15% oxygen to 34 healthy infants of whom 13 were the siblings of children who had died from sudden infant death syndrome.[5] The children were exposed to the hypoxic gas mixture for 6.3 (2.9) h. Four children developed 'prolonged and severe' episodes of desaturation. It is not possible to tell from the original paper exactly how low the oxygen saturations went. The average nadir of the saturations in each child was averaged and the lowest of these averages was 67%; presumably, individual episodes involved even more severe desaturation. The authors concluded that 'additional research is urgently needed into the effects on infants of prolonged airline flights or holidays at high altitude'.

Academic criticism of the hypoxia study

The paper was accompanied by an editorial[6] and a commentary criticising the study[7] and explanatory comments from the Chairman of the Ethical Committee.[8] There was subsequently extensive correspondence about the study, which was criticized on ethical and scientific grounds. Air travel confers a benefit against which parents can balance the risk of hypoxaemia but the research carried no potential benefit. There is no plausible mechanism to link airway hypoxia and Sudden Infant Death Syndrome. The methods used in the study were flawed and the data underanalysed and over-interpreted. Flying involves exposure to a low atmospheric pressure; the study used a normobaric hypoxic mixture.

Other issues

The review also took evidence about other research studies and the use of covert video surveillance to diagnose cases of Munchausen Syndrome by proxy.

Evidence given to the inquiry

Allegations from parents

Several parents made allegations concerning an inadequate or incomplete consent process. Specifically, they had no recollection of giving consent to randomization. CNEP was described to them as 'a kinder, gentler treatment whose alternative was pushing tubes down the baby'. Parents said they understood that they were consenting to a treatment but were not aware that they were consenting for entry into a research trial. Additional serious allegations included the suggestion that signatures on some consent forms may have been forged. But the review also heard evidence from another well conducted research study (of extracorporeal membrane oxygenation, ECMO[9]) that parents who have given well-documented consent may subsequently not recall having done so.

Evidence about research supervision

Evidence given to the review suggested that new guidelines for clinical research should be produced and supported by legislation. The duties of the Local Research Ethical Committee, LREC, should be extended to include monitoring of researchers including the receipt of regular formal reports with a formal process for accountability. An independent local medical inspectorate should be created. Arrangements should be made to follow-up research subjects after the conclusion of a study, to ensure that there are no unforeseen long-term problems. A proposal was made for a comprehensive review of research within the National Health Service.

Other proposals included log-books for individual researchers, a culture of routine self-audit amongst research teams and the use of independent third parties to obtain consent to research, particularly where this involves vulnerable groups of patients or a specially stressful situation where over-reliance on medical staff might be expected from anxious patients or relatives.

Guiding principles for those obtaining consent

The Nuremberg code

Written in 1947 in the aftermath of the war crimes tribunal, this sets the standard for obtaining consent from participants in research.[10] Key points are summarized in Table 1.

The Helsinki declaration

This was adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and has been updated and extended at subsequent meetings.[11] It extends and clarifies the Nuremberg code and interprets it in the context of biomedical research. Current proposals to update the Code are controversial.[12] Of relevance to anaesthesia is the debate about using placebos in clinical trials with one 'camp' arguing that efficacy can only be demonstrated with reference to a placebo and the other claiming that the only ethical control group is the current best therapy. The importance of this in the conduct of antiemetic studies has been extensively debated.[13 14]

Good clinical practice

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry to discuss scientific and technical aspects of product registration.[15] The objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Good Clinical Practice (GCP) is a set of guidelines published by ICH in 1996 which establish standards for the conduct of clinical trials.[16] These standards are in universal use by the pharmaceutical industry and have been adopted by major research funders such as the Medical Research Council. There is pressure for all 'own account' research to be conducted to GCP standards and whilst this is a worthy objective, those who call for this may be unaware of the resource implications for monitoring, audit and archiving.

Equipoise

Well-constructed research projects test an identifiable hypothesis. In theory, the researcher should be in a state of true equipoise, for example believing the probabilities of the hypothesis being true or false to be equal. In practice, this is virtually never true and it is frequently the case that researchers believe fervently in a particular scheme of treatment. Thus equipoise is a useful intellectual construct but is seldom encountered in practice; indeed, the ethical basis of equipoise itself has recently been questioned.[17] Given that researchers will always be enthusiastic about their own projects, an alternative may lie in the use of neutral third parties to explain research projects and obtain consent without the potentially biased enthusiasm of a committed researcher. Clearly, such third parties would require training and resources and any such requirement would likely inhibit a high proportion of low-cost studies and inflate the cost of others.

Current practice for obtaining consent to anaesthesia research

Consent for anaesthesia studies

Most patients scheduled for elective in-patient surgery are admitted to hospital the day before operation or, increasingly, on the same day. The interval between admission and surgery is a busy time with clerical procedures, physical examination and investigations to be completed. Current research practice includes the approaching of patients around the time of a pre-operative anaesthesia visit. Is this appropriate? What are the implications of change?

In 1998 we reported a survey of over 200 patients who had previously taken part in clinical trials run in our department.[18] Most patients (97%) were aware that participation was voluntary and that their care would not be affected by the decision to participate (98%) and that they could change their mind (83%). Only 25% would have liked longer to think about the trial and some patients made comments to the effect that knowing about the trial before admission would have caused them unnecessary worry. Overall, our data suggested that our patients had generally understood what they were consenting to with 95% describing the information supplied as an accurate description of what actually happened to them. We concluded that current practice of approaching patients shortly before surgery for participation in clinical trials of anaesthesia works well for most patients and there was little reason to make drastic changes. Indeed, to do so would grossly impair the conduct of such studies as surgical schedules are frequently changed at short notice and anaesthetists seldom have access to patients before their arrival at the hospital. Clearly, it would be wholly inappropriate to extrapolate from this data about patients undergoing elective surgical procedures to alternative environments including the labour ward and the intensive care unit.

Consent in obstetrics

Complex issues are raised when a woman is in labour. Whilst she is capable of consenting to or refusing interventions including epidural analgesia or Caesarean section, it is generally considered inappropriate to raise the question of participation in a research project for the first time during labour. It has therefore become customary to offer information about obstetric research projects to patients before they commence the labour. This may involve distribution of information at antenatal clinics or by other means. Whilst such dissemination is entirely practicable, it may have unanticipated consequences. When we offered information about a study of intrathecal diamorphine for obstetric analgesia to all women attending a hospital antenatal clinic, the result was large numbers of parturients asking to participate in the study at times when the investigators were not available with subsequent disappointment to patients who were keen to participate.[19]

Consent in intensive care

Most patients receiving intensive care are mentally impaired by drugs, by illness or both. Thus, this group is seldom legally competent to give informed consent for participation in a research study. Critical illness is usually unanticipated and advance consent to research is therefore impossible. How then can we obtain consent for research in intensive care? Different strategies exist which represent the interaction of national laws, investigator opinion and local ethical committees. Relatives of adult patients cannot give *consent* to a course of treatment; however, they may be consulted and give approval, for example *assent*. Courts can give consent but it is usual in the UK for participation in research to be allowed if it has been approved by the ethical committee. The assent of the patient's relatives is not legally necessary but it is customary in most, but not all, research active intensive care units to consult with relatives before patients are enrolled.

Research supervision

It is already the responsibility of senior researchers to monitor the activities of their teams and the risk taken by those who fail to do so is well known.[20]

Recommendations of the inquiry

The review recommended that formal guidance on research governance be developed with agreed guidance clarifying issues of consent for participation in clinical trials. A further recommendation proposed the establishment of a surveillance system for unexpected outcomes for non-drug treatments. Whilst these recommendations have no immediate effect on clinical researchers, when pursued, they may establish further formal and elaborate procedures, which must be followed by clinical researchers. The community of clinical researchers in anaesthesia must understand the direction of these changes and, where appropriate, ensure that their implications for our studies are anticipated.

How might this affect research in anaesthesia?

Consent

Consent was the key issue in the Stafford enquiry and we should reflect on how we obtain this in our own clinical trials. Anaesthetists have limited access to patients before surgery and obtaining consent has to be opportunistic. Nevertheless we must ensure that all research subjects have adequate time to discuss participation in a study before they give consent. Does this preclude consent on the day surgery unit or at the pre-operative visit on the night before surgery? Well-organized surgical specialties may bring their patients in for 'pre-clerking' several days before surgery. Others construct their operating lists at the last minute making it difficult to identify and obtain informed consent from surgical patients. The imposition of mandatory 'cooling off' periods has the potential to impair some clinical research. The timing and process of consent must be debated between researchers and their ethical committees with individual studies considered on a case-by-case basis. Researchers should be prepared to explain and defend their procedures.

What should we include on the consent form? In recent years patient information sheets and consent forms have been improved and in some regions standardized. When devising the wording of these documents we might usefully reflect on how it would read *post-hoc* at an inquiry! Properly worded explanations may be as useful as a patient advocate.

Who should take consent? Before we dismiss the researcher from this role we need to be clear that any proposed alternative is an improvement. Are third parties any better? Can a 'patient advocate' genuinely adopt a neutral role? Perhaps we should wait for this hypothesis to be rigorously evaluated in a trial of its own. At worst, a watered down and cheaply implemented version could leave us with ill informed SHO's or research nurses taking consent on behalf of their consultants or registrars.

Supervision

The responsibilities of researchers have been emphasized[20 21] and the role of the ethical committee explained.[22] At a time of intense public scrutiny of the medical profession we must be accountable for our research but who is to do the supervising? Ethics committees already monitor research but with their present resources they cannot police it. If they are to check and audit the research process they will require additional resources. What rules would determine the relationship between committee and researcher? Research ethics committees are not statutory bodies and establishment of a formal regulatory role would require legislation. These issues will need consultation before change is introduced or we may end up with unworkable law and unresourced supervisory bodies. Serving on an ethics committee is already hard work and ill-considered changes may make clinicians reluctant to participate.

Anaesthetists are well positioned to lead the debate in their own institutions. Ethical committees need advice from clinicians who understand pharmacology and who appreciate the context in which clinical research takes place. If we simply await the outcome of others deliberations we may find our research activities are crippled.

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Editorial IV

Local anaesthesia for eye surgery—no room for complacency

A recent article by Vohra and colleagues[1] reminds us that while regional anaesthesia for eye surgery is safe and reliable and complications are uncommon, there are a number of risk factors that predispose the globe to needle penetration during retrobulbar (RBA) and peribulbar (PBA) injections. The presence of a long eye, staphyloma or enophthalmos, the use of a faulty technique, a lack of appreciation of risk factors, an uncooperative patient and the use of an unnecessarily long needle are some of the contributory causes.[2] Patients presenting with axial myopia have a 30 times greater risk of globe puncture compared with patients with normal axial length.[2] A risk rate of one perforation for every 140 peribulbar blocks in eyes with an axial length greater than 26 mm has been calculated.[2]

Interestingly, an increase in axial length is associated with only a marginal increase in equatorial width.[1] Vohra and colleagues[1] have suggested that in patients with axial length greater than 26 mm, the medial canthal route for PBA injection might be safer than the inferotemporal route as the inferotemporal quadrant of the globe is the commonest reported site of perforation after RBA and traditional PBA blocks. This is not surprising as the majority of blocks are performed using the inferotemporal route. From their survey,[3] and by extrapolation of data from the National Cataract Surgery Survey,[4] Gillow and colleagues estimate that the overall incidence of ocular perforation during cataract surgery under local anaesthesia is about 0.114%. A much lower ocular perforation incidence of 1:16 224 PBA blocks was reported by Davis and Mandel.[5] Nicoll[6] reported a series of 6000 RBA injections. Sixteen patients (1 in 375) had complications that suggested direct spread of the anaesthetic agent via the dural cuff into the central nervous system. Other serious complications reported with RBA block include damage to the optic nerve and retrobulbar haemorrhage. These reports have resulted in a search for safer methods of local anaesthesia. Descriptions of PBA block,[7] simplified and safer PBA block,[8] sub-Tenon's block,[9] subconjunctival injection[10] and topical anaesthesia[11] have all appeared in the literature.

Ten years ago, very few anaesthetists in the UK were performing local anaesthetic blocks for eye surgery. At that time, anaesthetists did not feel confident placing needles deep in the orbit because of the potential complications. Most operations were performed under general anaesthesia. On the rare occasions where a local anaesthetic was indicated, the surgeons did the RBA injection themselves, and often demanded a degree of sedation indistinguishable from a general anaesthetic, surely the worst choice for poor risk patients. The surgeons' RBA block involved injecting a small volume of local anaesthetic often through a relatively wide bore (up to 21 g) and very long (up to 5 cm) needle. This meant that the injection was made inside the extra-ocular muscle cone and close to the orbital apex where most of the vital structures are situated.

By 1990, there was increasing interest among anaesthetists in promoting the change to local anaesthesia, especially for cataract surgery.[12] Peribulbar block had been described[7] and much shorter needles 2.5–3 cm were being used so that local anaesthetic was deposited outside the muscle cone and often no deeper than the globe equator. This was believed to be much safer, reducing the incidence of most of the complications of the traditional RBA block.[5] Anaesthesia, akinesia and operating conditions were said to be adequate provided enough time was allowed for the larger volume of local anaesthetic to diffuse from the site of injection into the muscle cone where most of the sensory and motor nerves and the ciliary ganglion are situated. Anaesthetists embarked on this technique either using the Davis and Mandel[7] description or a modification of it. Often anaesthetists were supervised initially by surgeons who themselves had limited experience of the techniques and were fearful of the consequences of this invasion of their territory by specialists who understood veins and airways but might have limited knowledge of orbital anatomy.[13] There was a definite learning curve, the first attempts often leading to very long onset times of at least 20 min, and inadequate or even failed blocks. Repeated supplementary injections in the inferotemporal, nasal or superotemporal regions were often necessary to achieve success. The nasal compartment block[14] was adopted widely and was found to supplement the quality of the inferotemporal block, and by filling the lids and blocking the terminal branches of the facial nerve made the classical facial nerve block obsolete.

Progressively as more experience was gained, the PBA block seemed to work quicker, the quality of the block was better and the success rate was higher. The question, of course, was whether this inferotemporal block was in fact still a PBA block or something else. The needles, while still only 2.5 cm long, were, after passing the equator, moving upwards and inwards. A wide range of local anaesthetic injection techniques were used, some of which may be described as retrobulbar by one clinician and peribulbar by another.[15] New names, such as posterior bulbar, or anterior and shallow retrobulbar block, were appearing. It seemed that the rapid onset and improved block quality excluded an extraconal injection, and in spite of the shorter needle length the needle tip had to be intraconal. If larger volumes were used, a second injection might not be required, increasing safety. The increasing use of PBA block over the last decade or so is attributable to its reputation for a reduced risk of serious complications compared to RBA block. But if the new PBA is an intraconal injection it may have the potential for all the complications reported with the traditional RBA approach. So what are the alternatives available to the anaesthetist?

To avoid injections deep into the orbit, topical anaesthesia and subconjunctival anaesthesia have been advocated, the latter involving a subconjunctival injection of anaesthetic at the 12 o'clock position.[10] Neither of these techniques reduce globe movement. Topical anaesthesia is particularly popular in the USA where it was used in 30% of all cataract operations in 1998.[16] Advances in surgical techniques, such as small incision phaeco-emulsification, which have lessened the need for akinesia during surgery, may account for its popularity. However, topical anaesthesia results in significantly higher pain scores compared with sub-Tenon's anaesthesia so that surgery is more stressful for both patient and surgeon.[17] Chittenden[17] found that with topical anaesthesia application of cautery to scleral vessels was particularly painful. Topical anaesthesia may, therefore, be more appropriate when cataract surgery is done through a clear corneal incision. With experienced surgeons, short, uncomplicated procedures and carefully selected patients, topical anaesthesia is very effective with no tissue invasion and therefore no local complications. It saves time, wears off rapidly so that eye padding is not required and the visual result is immediately apparent. However, it requires more patient co-operation to keep the eye relatively still, or the use of two instruments in the eye at 90° to each other to immobilize it. Moreover, only the front of the eye is anaesthetized and the patient will experience pain if the iris or the ciliary body is touched. In the USA topical anaesthesia is often combined with i.v. sedation.[18] In the UK the use of sedation is rare, most patients being managed by verbal interaction, explanation and reassurance. Increasing use of sedation would counterbalance the increased safety attributed to topical anaesthesia. No increase in the use of sedation was found in the National Survey published in 1999.[15] But surgeons are reluctant to operate without adequate ocular akinesia. There are thus many occasions when for various reasons, either an alternative local anaesthetic technique providing good akinesia or even general anaesthesia is indicated.

Sub-Tenon's block offers such an alternative. Access to the sub-Tenon's space may be obtained through different approaches. The inferior nasal quadrant approach[9] is popular in the UK. Anatomically, this approach is less likely to cause complications compared to the inferotemporal approach.[9] Four quadrant techniques have been used especially for vitreoretinal surgery.[19]

Sub-Tenon's block was reported to be completely painless by 99.1% of patients.[20] Thus, the sharp rises in arterial pressure and associated dysrrhythmias reported with painful procedures do not occur with the sub-Tenon's block.[21] In the same study, 97.3% patients did not have any pain during surgery. This block has been found to be effective for cataract surgery, pan-photocoagulation,[22] vitreo-retinal surgery,[19] and strabismus surgery.[23] But the degree of akinesia varies. Differences in the choice of local anaesthetic, the volume injected and the time allowed for it to take effect can explain this variation. Limited akinesia was reported using 1.5 ml of 2% lidocaine solution while complete akinesia was achieved at 15 min using up to 4 ml of a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine.[21] Because of the smaller volumes of local anaesthetic used, akinesia of the orbicularis oculi is not always achieved. Thus, it has the advantage of producing moderate to good akinesia, excellent anaesthesia and by using a blunt cannula rather than a sharp needle reduces the chance of needle related complications. Indeed, in a study of 3000 sub-Tenon's blocks[24] no systemic or orbital complications were reported. It may be reinforced at any time during surgery, although this is rarely required if a local anaesthetic of suitable duration is used. Among the complications of the technique, chemosis is common but the solution disperses quickly and does not interfere with surgery. Similarly, subconjunctival haemorrhage is frequently caused from fine vessels, which may be severed on making the small conjunctival incision.

What about patients on anticoagulants? A case could be made for general anaesthesia as subconjunctival haemorrhage is common with the sub-Tenon's block. On the other hand, the bleeding is from conjunctival or episcleral vessels and can be controlled with pressure and patience. There is a risk of damage to a vortex vein, which might lead to considerable bleeding.[8] If a local anaesthetic technique is chosen, a sub-Tenon's block with a blunt cannula should be safer than a sharp needle local anaesthetic technique.

Opinions regarding pre-operative preparation of patients for surgery under local anaesthesia have changed over the last decade. Traditionally, presumably because the incidence of complications with the RBA was significant, patients were prepared similarly to those for general anaesthesia. In 1990 Rubin wrote, 'patients should be fasted, investigated and prepared as fully as for a general anaesthetic'.[12] Most centres these days do not starve their patients and routine investigations are omitted before surgery under local anaesthesia. Intravenous access and monitoring including electrocardiogram, non-invasive arterial pressure measurement and pulse oximetry should always be used. This requires the presence of someone able to interpret the measurements, and seek help when necessary.

In their report in 1992, the Joint College of Ophthalmologists and The Royal College of Anaesthetists Working Party[25] recommended that an anaesthetist should be present during ocular surgery under local anaesthesia. At that point they were acutely aware of the potential complications with the RBA block. Nearly 10 yr later with the incidence of serious complications much reduced, with wide experience of PBA, and with the excellent safety record of the sub-Tenon's block, which is fast growing in popularity, is the presence of an anaesthetist still appropriate? By the time this editorial is published the second report of the joint Royal College of Ophthalmologists and The Royal College of Anaesthetists Working Party, due early in 2001, will have answered this question for us, advising that an anaesthetist is only essential if PBA or RBA is used or sedation is given.

In conclusion, PBA or shallow RBA blocks are very safe unless there are risk factors. When risk factors are present, topical anaesthesia or sub-Tenon's blocks might be safer. Each of the different local anaesthetic blocks for eye surgery has its indications. At times, general anaesthesia is the best choice. Patients should have the benefit of the most appropriate technique administered by properly trained personnel.

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BJA

CLINICAL INVESTIGATIONS

Effect of changes in arterial-mixed venous oxygen content difference ($C(\text{a}-\bar{\text{v}})_{\text{O}_2}$) on indices of pulmonary oxygen transfer in a model ARDS lung†,††

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Many indices are used to quantify pulmonary oxygen transfer. Indices that use only measurements from arterial blood and inspired gas assume a constant $C(\text{a}-\bar{\text{v}})_{\text{O}_2}$. Though variations in $C(\text{a}-\bar{\text{v}})_{\text{O}_2}$ are recognized, indices such as $Pa_{\text{O}_2}/FI_{\text{O}_2}$ remain popular and are often considered the best measure of pulmonary oxygen transfer in critically ill patients. This study estimated the effect of within-subject variations in $C(\text{a}-\bar{\text{v}})_{\text{O}_2}$ and FI_{O_2} on venous admixture ($\dot{Q}s/\dot{Q}t$), the calculated oxygen content difference between end-capillary and arterial blood ($Cc'_{\text{O}_2}-Ca_{\text{O}_2}$), the alveolar–arterial oxygen tension gradient ($P(\text{A}-\text{a})_{\text{O}_2}$) and $Pa_{\text{O}_2}/FI_{\text{O}_2}$, using a validated lung model of acute respiratory distress syndrome (ARDS). All four indices showed changes with FI_{O_2} and $C(\text{a}-\bar{\text{v}})_{\text{O}_2}$, although the magnitude of changes in $\dot{Q}s/\dot{Q}t$ was clinically unimportant (<2%). The other three indices showed larger variations that may potentially be misleading. At an FI_{O_2} of 0.7, $Pa_{\text{O}_2}/FI_{\text{O}_2}$ varied between 18 and 10 kPa and at an FI_{O_2} of 0.9 the ratio varied between 22 and 8 kPa. These changes, which were unrelated to underlying lung pathology, are sufficiently large to result in misclassification on the gas exchange scale suggested by the American European Consensus Conference on ARDS. This study shows there is no reliable alternative to $\dot{Q}s/\dot{Q}t$ to quantify pulmonary oxygen transfer in critically ill patients.

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Several oxygen tension and content-based indices are used to quantify pulmonary oxygen transfer. Tension-based indices include the alveolar–arterial oxygen tension gradient ($P(\text{A}-\text{a})_{\text{O}_2}$), the ratio ($Pa_{\text{O}_2}/FI_{\text{O}_2}$) between arterial oxygen tension (Pa_{O_2}) and fractional inspired oxygen (FI_{O_2}), the respiratory index ($P(\text{A}-\text{a})_{\text{O}_2}/Pa_{\text{O}_2}$) and the arterial–alveolar oxygen tension ratio ($Pa_{\text{O}_2}/PA_{\text{O}_2}$). Indices such as venous admixture ($\dot{Q}s/\dot{Q}t$), the estimated shunt fraction (which gives the arterial–mixed venous oxygen content difference a fixed value) and the calculated content difference between end-capillary and arterial blood ($Cc'_{\text{O}_2}-Ca_{\text{O}_2}$) are based on oxygen content. The relationship between partial pressure and oxygen content in blood is non-linear and therefore indices that use oxygen tension may be disproportionately dependent on FI_{O_2}, particularly in patients with intrapulmonary shunting.[1–3] The relationship between $\dot{Q}s/\dot{Q}t$ and FI_{O_2} is also not straightforward. Douglas *et al.* showed that $\dot{Q}s/\dot{Q}t$ was largest with FI_{O_2}=0.21, least with FI_{O_2} from 0.4 to 0.6 and increased again for FI_{O_2} >0.6.[4] Gowda *et al.* showed that variations in $\dot{Q}s/\dot{Q}t$ related to FI_{O_2} were directly proportional to the fraction of cardiac output perfusing alveolar units with a low ventilation/perfusion ratio ($\dot{V}/\dot{Q}$).[5]

The difference in oxygen content between arterial and mixed venous blood ($C(\text{a}-\bar{\text{v}})_{\text{O}_2}$) is an important variable in the assessment of pulmonary oxygen transfer. Although considerable within- and between-patient variability is

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common in critical illness,[6] indices such as Pa_{O_2}/FI_{O_2} remain popular for clinical and research purposes. Furthermore, the inclusion of Pa_{O_2}/FI_{O_2} in the American European Consensus Conference recommendations on acute respiratory distress syndrome (ARDS)[7] has led to the widespread impression that the Pa_{O_2}/FI_{O_2} ratio is the preferred method of assessing pulmonary oxygen transfer in clinical studies.[8] For example, in a recent multicentre trial on inhaled nitric oxide, the efficiency of pulmonary oxygen transfer was assessed over several days using Pa_{O_2}/FI_{O_2}, no data or comment being provided on variations in mixed venous oxygen content that may have influenced the findings.[9] This approach compromises the critical evaluation of the effects of a given intervention on pulmonary oxygen transfer.

Direct assessment of the effect of $C(a-\bar{v})_{O_2}$ involves manipulation of the delicate physiological balance that is frequently seen in critically ill patients, and raises difficult ethical issues. Mathematical models have therefore been considered appropriate tools to address similar problems.[1 5] Such models require formal validation if conclusions are to receive wider acceptance.

This study was therefore undertaken, with the following objectives: (i) to describe and validate a mathematical model of an ARDS lung; and (ii) to use the above model in a theoretical study evaluating the effect of $C(a-\bar{v})_{O_2}$ and FI_{O_2} on four commonly used indices of pulmonary oxygen transfer.

Materials and methods

The study was carried out in two stages: in stage 1 a lung model of ARDS was described and validated, and stage 2 consisted of a theoretical appraisal of four commonly used indices of pulmonary oxygen transfer.

Stage 1: lung model of ARDS

To derive a lung model of ARDS, a multicompartment model of a normal lung[10 11] was modified by incorporating data on shunt, dead space and $\dot{V}/\dot{Q}$ scatter obtained by Dantzker *et al.* in patients with ARDS[12] (Appendix 1). Validity of the model was verified using new data collected from 10 consecutive patients treated for ARDS in our intensive care unit. After institutional approval had been obtained, between four and seven sets of arterial and mixed venous blood gas measurements and cardiac output estimations were obtained from each patient. The following measurements were recorded: Pa_{O_2}, Pa_{CO_2}, arterial haemoglobin saturation (Sa_{O_2}), mixed venous oxygen tension ($P\bar{v}_{O_2}$), mixed venous carbon dioxide tension ($P\bar{v}_{CO_2}$), mixed venous haemoglobin saturation (Sv_{O_2}), haemoglobin concentration (Hb), venous admixture ($\dot{Q}s/\dot{Q}t$), cardiac output and fractional inspired oxygen (FI_{O_2}). The position of the pulmonary artery catheter was confirmed radiologically and all blood gas/cardiac output measurements were made by trained nursing staff. The blood gas machine and co-oximeter (BGE and IL282 respectively; Instrumentation Laboratory, Milan, Italy) were calibrated according to the manufacturer's guidelines. Cardiac output, $\dot{Q}s/\dot{Q}t$, Hb, $P\bar{v}_{O_2}$, Sv_{O_2}, $P\bar{v}_{CO_2}$ and FI_{O_2} for each set of readings were used as input variables to obtain a predicted Pa_{O_2} through an iterative process.

Pa_{O_2} predicted by the model and the true (measured) Pa_{O_2} were compared by analysis of covariance (ANCOVA) to determine the within-subject correlation coefficient (*r*). Agreement was assessed using the intraclass correlation coefficient (r_I)[13] and Bland–Altman analysis.[14]

Stage 2: evaluation of indices of pulmonary oxygen transfer

After validation, the lung model was used to derive four commonly used indices of pulmonary oxygen transfer ($\dot{Q}s/\dot{Q}t$, $Cc'_{O_2}-Ca_{O_2}$, $P(A-a)_{O_2}$ and Pa_{O_2}/FI_{O_2}) as FI_{O_2} was varied between 0.21 and 1.0. We assumed constant minute ventilation, temperature (37°C), acid–base balance (base excess=0) and respiratory exchange ratio (RER=0.85) and a normal oxygen dissociation curve (P_{50}=3.6 kPa). The oxygen content of arterial blood (Ca_{O_2}) was determined by weighting of compartmental perfusion and ventilation. Mixed venous oxygen content ($C\bar{v}_{O_2}$) was derived from Ca_{O_2} and peripheral oxygen extraction. End-capillary oxygen content was derived in the customary fashion using the alveolar gas equation.[3] The process was repeated for three fixed $C(a-\bar{v})_{O_2}$ values: 22.0, 35.6 and 49.2 ml litre^{-1}. This range represents the mean ± two within-subject standard deviations for $C(a-\bar{v})_{O_2}$ in critically ill patients.[6] Patient data used for validation of the model were not used in deriving any of the indices.

Results

Stage 1: lung model

Blood gas data from the 10 ARDS patients used in the validation of the model are given in Appendix 2. Figure 1 shows the distribution of $\dot{V}/\dot{Q}$ in the model lung. Shunt ($\dot{V}/\dot{Q}$ <0.005) and dead space ($\dot{V}/\dot{Q}$ >100) were 40.7 and 28.8% respectively. Approximately 10% of cardiac output perfused units with $\dot{V}/\dot{Q}$ <0.1. ANCOVA returned r=0.93 (r^2=0.86, P<0.001). Intraclass correlation assessed by r_I was 0.91. Bland–Altman analysis showed a bias (measured minus predicted) of 1 kPa with limits of agreement of −2 to +4 kPa.

Stage 2: evaluation of indices of pulmonary oxygen transfer

Venous admixture ($\dot{Q}s/\dot{Q}t$)

Figure 2 shows changes in $\dot{Q}s/\dot{Q}t$ when FI_{O_2} was altered from 0.21 to 1.0. In the entire range of FI_{O_2} the maximum

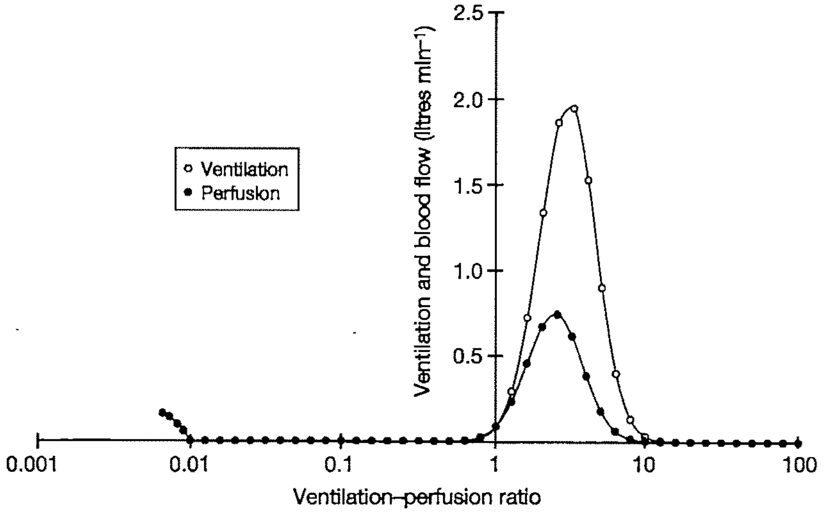

Fig 1 Distribution of ventilation–perfusion in the ARDS lung model.

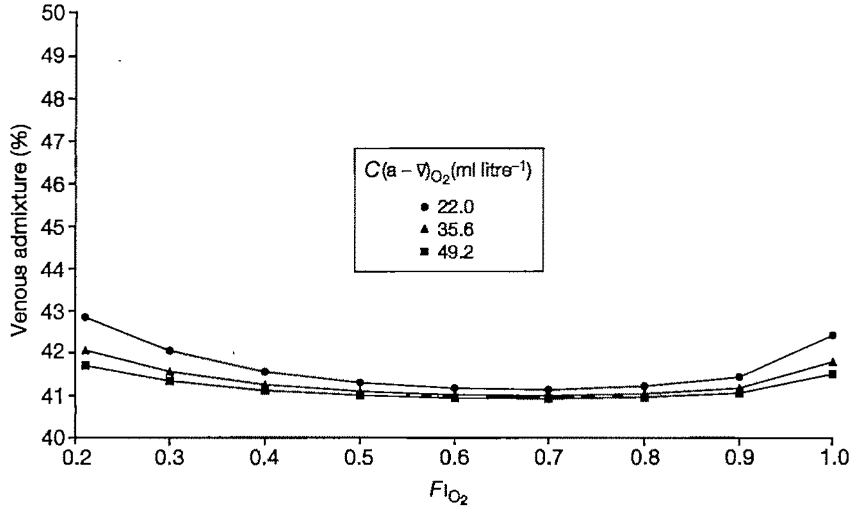

Fig 2 Venous admixture as a function of $F\mathrm{I}_{O_2}$.

difference noted in $\dot{Q}s/\dot{Q}t$ due to variation in $C(a–\bar{v})_{O_2}$ was approximately 1%, with lesser changes noted at higher $F\mathrm{I}_{O_2}$ ($F\mathrm{I}_{O_2}$=0.5–0.9). At constant $C(a–\bar{v})_{O_2}$ the change in $\dot{Q}s/\dot{Q}t$ due to $F\mathrm{I}_{O_2}$ was less than 2%, and these differences were also less at higher $F\mathrm{I}_{O_2}$.

Difference between end-capillary and arterial oxygen content (Cc'_{O_2}–Ca_{O_2})

Figure 3 shows the changes in Cc'_{O_2}–Ca_{O_2}. All three curves showed a similar trend, with a reduction in Cc'_{O_2}–Ca_{O_2} by a maximum of 1.1 ml litre^{-1} when $F\mathrm{I}_{O_2}$ was increased from 0.21 to 1.0. Approximately 90% (1.0 ml litre^{-1}) of this change occurred in the $F\mathrm{I}_{O_2}$ range 0.21–0.5. However, the difference between the curves at different levels of $C(a–\bar{v})_{O_2}$ was up to 19 ml litre^{-1}.

Ratio of Pa_{O_2} to $F\mathrm{I}_{O_2}$

Figure 4 shows the relationship between $Pa_{O_2}/F\mathrm{I}_{O_2}$, $F\mathrm{I}_{O_2}$ and $C(a–\bar{v})_{O_2}$. When $F\mathrm{I}_{O_2}$ was increased from 0.21 to 0.9 the corresponding ratio decreased from 29 to 11 kPa ($C(a–\bar{v})_{O_2}$=35.6 ml litre^{-1}). The curves tended to flatten out in the $F\mathrm{I}_{O_2}$ range of 0.5–0.8, changes being less than 5 kPa for all three curves. The relationship with $F\mathrm{I}_{O_2}$ was more complex when $C(a–\bar{v})_{O_2}$ was low (22 ml litre^{-1}), as the ratio increased again when $F\mathrm{I}_{O_2}$>0.7.

Alveolar–arterial oxygen tension gradient ($P(\mathrm{A}–a)_{O_2}$)

Figure 5 summarizes the relationship between $P(\mathrm{A}–a)_{O_2}$, $F\mathrm{I}_{O_2}$ and $C(a–\bar{v})_{O_2}$. The changes in $P(\mathrm{A}–a)_{O_2}$ due to $C(a–\bar{v})_{O_2}$ ranged between 2.1 and 12.2 kPa. The changes with $F\mathrm{I}_{O_2}$ were considerable, increased $F\mathrm{I}_{O_2}$ resulting in a proportionate increase in $P(\mathrm{A}–a)_{O_2}$.

Discussion

The inability to define a unique continuous distribution of $\dot{V}/\dot{Q}$ scatter using inert gas elimination is well recog-

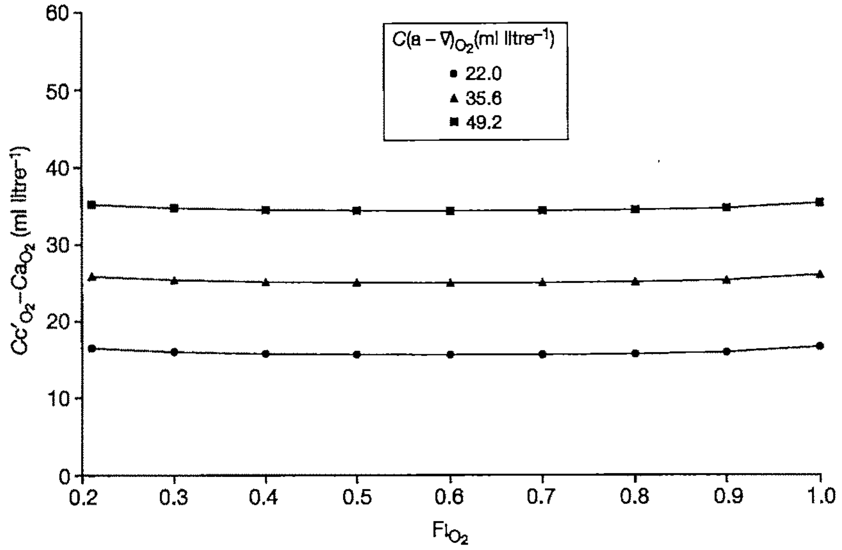

Fig 3 Cc'_{O_2}–Ca_{O_2} as a function of FI_{O_2}.

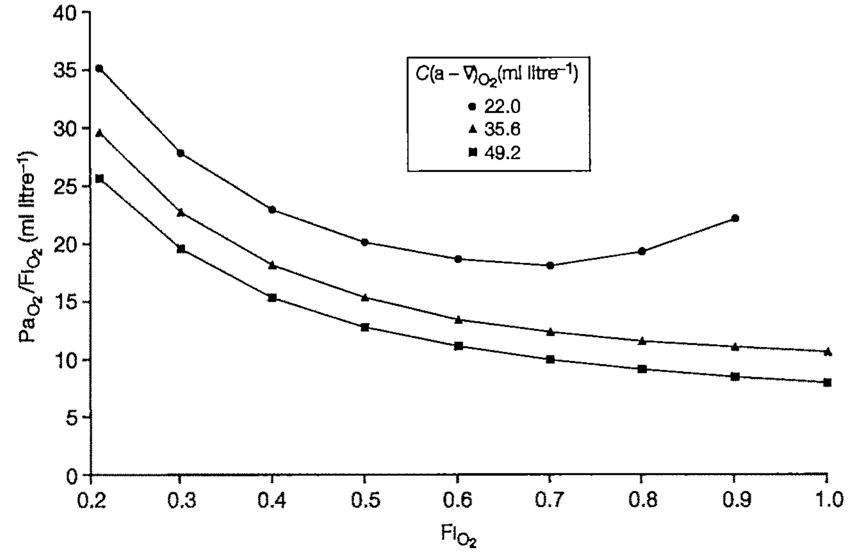

Fig 4 Pa_{O_2}/FI_{O_2} as a function of FI_{O_2}.

nized.[15] [16] Nevertheless, multicompartment models represent the extensive spread of $\dot{V}/\dot{Q}$ scatter seen in disease states satisfactorily and are accepted tools in pulmonary research.[5] [17] Measured $\dot{Q}s/\dot{Q}t$ in the data used for validation of the model (Appendix 2) includes true shunt and a further contribution due to $\dot{V}/\dot{Q}$ mismatch. This fraction was considered equal to the true shunt in each patient as it was not possible to separate the two components. Because FI_{O_2} was always >0.5, any contribution from $\dot{V}/\dot{Q}$ mismatch to measured $\dot{Q}s/\dot{Q}t$ is expected to be minimal. This explains the good correlation between measured and predicted Pa_{O_2} (r=0.93).

The model does not account for effects of FI_{O_2} on pulmonary vascular autoregulation, which is an important physiological compensatory mechanism[18] and may account for the underestimation of Pa_{O_2} by the model. The effects of metabolic acidosis/alkalosis, temperature and 2,3-diphosphoglycerate (2,3-DPG) on the oxyhaemoglobin dissociation curve and the effects of abnormal forms of haemoglobin on pulmonary oxygen transfer have also not been modelled. The above factors may account for the relatively wide limits of agreement seen in the study. In spite of these limitations, the model is sufficiently accurate (r= 0.93, r_i=0.91, bias=+1 kPa, SD=1.5 kPa) to justify its use. The difficulties in measuring high Pa_{O_2} using standard oxygen electrodes is well known. However, the range of Pa_{O_2} values in our patients (3.3–27 kPa) was well within the stipulated measuring range for the blood gas machine

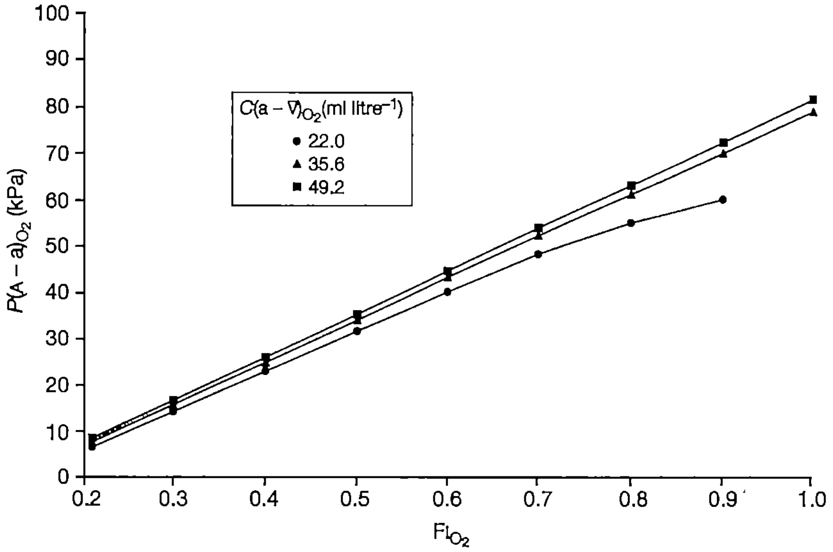

Fig 5 $P(\text{A}-\text{a})_{O_2}$ as a function of $F\text{I}_{O_2}$.

(0–106 kPa). Therefore, measurement errors are unlikely to have contributed to any of the observed discrepancies. In deriving the indices of pulmonary oxygen transfer, a fixed shunt (true shunt) was assumed despite changes in $F\text{I}_{O_2}$. It is well recognized that in patients with a large contribution from areas with $\dot{V}/\dot{Q}$ mismatch, changes in $F\text{I}_{O_2}$ lead to changes in $\dot{Q}s/\dot{Q}t$. Our model describes these changes well (Fig. 2). The absorption atelectasis that may occur in the presence of high $F\text{I}_{O_2}$, on the other hand, may lead to increased shunting. However in order to quantify the effects of extrapulmonary factors such as $F\text{I}_{O_2}$ and $C(\text{a}-\bar{\text{v}})_{O_2}$ on the indices, it was necessary to hold the intrapulmonary factors (shunt, $\dot{V}/\dot{Q}$ scatter and dead space) constant. Absorption atelectasis was therefore not included in the present model.

Oxygen tension based indices

Indices based on Pa_{O_2} may be popular because they are simple. In patients with normal lungs, stable cardiovascular status and constant peripheral oxygen extraction, good correlation has been demonstrated between $\dot{Q}s/\dot{Q}t$ and $Pa_{O_2}/F\text{I}_{O_2}$ or $P(\text{A}-\text{a})_{O_2}$.[1 19 20] In a theoretical study, Rasanen *et al.* demonstrated the relationship between $\dot{Q}s/\dot{Q}t$ and these three indices to be non-linear and greatly influenced by $F\text{I}_{O_2}$ and $C(\text{a}-\bar{\text{v}})_{O_2}$.[1] The range of $C(\text{a}-\bar{\text{v}})_{O_2}$ used by Rasanen *et al.* (20–80 ml litre^{-1}) was, however, arbitrary and therefore the study failed to convince many clinicians of the disadvantages of indices such as $Pa_{O_2}/F\text{I}_{O_2}$. We have therefore revisited the subject to determine whether the range of variation that is known to occur within individual patients[6] is small enough to justify the continued use of indices such as $Pa_{O_2}/F\text{I}_{O_2}$.

The disadvantage of using $P(\text{A}-\text{a})_{O_2}$ to quantify pulmonary oxygen transfer is evident from Fig. 5. On the other hand, $Pa_{O_2}/F\text{I}_{O_2}$ is a simple index and has gained widespread acceptance for clinical and research purposes.[7 8 21] A review of the literature shows conflicting data on the accuracy with which $Pa_{O_2}/F\text{I}_{O_2}$ reflects $\dot{Q}s/\dot{Q}t$. Some studies have shown good correlation in groups of critically ill patients, and the evidence presented forms the basis for its current popular use.[2 5 19 23] Other studies, however, show poor correlation.[24–26] Because of the inclusion of multiple readings obtained from individual patients with a variety of illnesses, the correlation coefficients cited in studies comparing $Pa_{O_2}/F\text{I}_{O_2}$ and $\dot{Q}s/\dot{Q}t$[2 19 23 24] may be erroneously high and not reflect the true relationship between the two indices.[27] Nevertheless, there is no doubt that $Pa_{O_2}/F\text{I}_{O_2}$ is a useful clinical parameter as long as the underlying assumptions are appreciated and regularly evaluated. In the present study most of the observed $F\text{I}_{O_2}$-related variations were at low $F\text{I}_{O_2}$, and in the 0.5–0.8 range variability was less than 5 kPa. The relationship between $Pa_{O_2}/F\text{I}_{O_2}$ and $F\text{I}_{O_2}$ is more complex when $C(\text{a}-\bar{\text{v}})_{O_2}$ is low (22 ml litre^{-1}), a condition likely in septic patients with a hyperdynamic circulation. Under these circumstances, $Pa_{O_2}/F\text{I}_{O_2}$ increases when $F\text{I}_{O_2}>0.7$. The problem may be compounded by changes in $C(\text{a}-\bar{\text{v}})_{O_2}$ at the same time. For example, when $F\text{I}_{O_2}=0.7$ the ratio varied between 18 and 10 kPa with changes in $C(\text{a}-\bar{\text{v}})_{O_2}$, and when $F\text{I}_{O_2}=0.9$ the ratio varied between 22 and 8 kPa. These changes are large enough to result in misclassification on the gas exchange scale suggested by the American European Consensus Conference.[7] Despite this, a recent review quoting Gowda *et al.* states that the $Pa_{O_2}/F\text{I}_{O_2}$ ratio is 'the preferred method of assessing gas exchange in clinical trials'.[8] The group of patients represented by Gowda *et al.* in their theoretical models, in reality, represents patients likely to require many interventions that lead to changes in $C(\text{a}-\bar{\text{v}})_{O_2}$. This limits the usefulness of $Pa_{O_2}/F\text{I}_{O_2}$

in this patient group. What is not disputed is that Pa_{O_2}/FI_{O_2} is not an objective marker of pulmonary oxygen transfer in patients with haemodynamic and metabolic instability. It therefore follows that Pa_{O_2}/FI_{O_2} in ARDS should be interpreted with caution, particularly when pulmonary oxygen transfer is assessed over several days.

Indices based on oxygen content

$\dot{Q}s/\dot{Q}t$ derived at the clinically chosen FI_{O_2} is a widely used method and has been used as the gold standard measure of pulmonary oxygen transfer.[2 19 23] By comparing calculated $\dot{Q}s/\dot{Q}t$ at FI_{O_2} of 0.5 and 1.0, Gowda *et al.* demonstrated that the variability in $\dot{Q}s/\dot{Q}t$ (related to FI_{O_2}) was directly proportional to the fraction of cardiac output perfusing alveolar units with $\dot{V}/\dot{Q}$ ratios of less than 0.1.[5] Therefore, the relative contribution to $\dot{Q}s/\dot{Q}t$ from shunt and areas of low but finite $\dot{V}/\dot{Q}$ is an important determinant of the variability in $\dot{Q}s/\dot{Q}t$ with FI_{O_2}. In the present study, although approximately 10% of cardiac output perfused alveolar units with $\dot{V}/\dot{Q}$ <0.1, the magnitude of changes in $\dot{Q}s/\dot{Q}t$ due to variation in $C(a-\bar{v})_{O_2}$ or FI_{O_2} was small (<2%) and clinically unimportant. Rossaint *et al.*[17] demonstrated a similar distribution of ventilation and perfusion in a study of 12 ARDS patients (shunt, 35%; flow to areas of lung with $\dot{V}/\dot{Q}$ <0.1, 10%; dead space, 34%). In a more recent study, Santos *et al.* confirmed that the primary mechanism for impaired pulmonary oxygen transfer in patients with acute lung injury was right-to-left shunt and blood flow to alveolar units with $\dot{V}/\dot{Q}$ <0.1 less than 10%.[28] In the absence of mixed venous blood samples, Kerr in 1975[29] and Drummond and Zhong in 1983[30] used $Cc'_{O_2}-Ca_{O_2}$ to quantify pulmonary oxygen transfer in clinical studies conducted in stable patients over relatively short periods. The present study confirms that variation in $C(a-\bar{v})_{O_2}$ limits its clinical application.

The ventilation/perfusion distribution shown in our model has important implications in the management of patients with ARDS. Simply increasing FI_{O_2} beyond 0.5 may not achieve worthwhile improvements in arterial oxygen content, because the contribution from $\dot{V}/\dot{Q}$ mismatch to $\dot{Q}s/\dot{Q}t$ is almost completely eliminated at an FI_{O_2} of approximately 0.5.[3] If right-to-left shunting is the dominant cause of abnormal pulmonary oxygen transfer, then further increases in FI_{O_2} do not compensate for this defect.[3] Measures that are intended to achieve a reduction in shunt, such as higher positive end-expiratory pressure and prone position, are more appropriate and should be considered early in patients with ARDS if adequate arterial oxygen content is not achieved with FI_{O_2} above 0.5.

In conclusion, in ARDS there may be marked cardiorespiratory and metabolic abnormalities resulting from the underlying disease and/or interventions. In such patients, there is no reliable substitute for $\dot{Q}s/\dot{Q}t$ to quantify defects in pulmonary oxygen transfer. There is also a need to clarify the criteria used in research in which interventions that may influence pulmonary oxygen transfer are assessed over relatively long periods. We believe that the inclusion of Pa_{O_2}/FI_{O_2} in the American European Consensus Conference recommendations without qualification may lead to its inappropriate use.

Acknowledgement

We thank the medical, nursing and technical staff of the intensive care unit at Withington Hospital, Manchester for their support in this study.

Appendix 1: ARDS lung model

Modelling of pulmonary oxygen transfer

A numerical method based on the early work on this subject by Wallace Fenn *et al.* and described in greater detail by West[31] was used to calculate gas exchange in individual lung compartments. The oxygen–carbon dioxide (O_2–CO_2) diagram and the ventilation/perfusion ratio $\dot{V}A/\dot{Q}C$ line (where $\dot{V}A$ is the alveolar ventilation and $\dot{Q}C$ is the pulmonary capillary blood flow), which describes all possible alveolar compartments that can exist within a lung at any given time, forms the cornerstone of this model. In order to derive the ventilation/perfusion ratio line, it is necessary to solve the following $\dot{V}A/\dot{Q}C$ ratio equation:[32]

$$\dot{V}\mathrm{A}/\dot{Q}\mathrm{C} = \frac{8.63(C\bar{v}_{CO_2} - Cc'_{CO_2})}{P\mathrm{A}_{CO_2}} \qquad (1)$$

where $C\bar{v}_{CO_2}$ and Cc'_{CO_2} refer to the carbon dioxide concentration of mixed venous blood and end-capillary blood respectively, in units of ml dl^{-1}, and PA_{CO_2} is the alveolar partial pressure of carbon dioxide in mm Hg. In solving the above equation it is necessary to take into account the Haldane and Bohr effect, whereby the relationship between partial pressure and the end-capillary concentrations of carbon dioxide and oxygen in the blood draining from each compartment alters with changes in $\dot{V}A/\dot{Q}C$. Because the equations defining the oxygen and carbon dioxide dissociation curves are non-linear and interdependent, an iterative procedure incorporating a root-finding algorithm based on bracketing and bisection[33] was used in deriving the solution. The method was used to find a common solution for compartmental ventilation, compartmental blood flow and the end-capillary concentration of oxygen and carbon dioxide in the blood draining from each of the compartments. This iterative process was stopped when the oxygen saturation on the oxygen and carbon dioxide dissociation curves agreed within 0.001%.

The oxygen dissociation curve was described by the Hill function:[34]

Table 1 Data used to validate the ARDS lung model

Patient	$\dot{Q}s/\dot{Q}t$ (%)	Cardiac output (litre min–1)	FI_{O_2}	Hb (g dl^{-1})	$P\bar{v}_{O_2}$ (kPa)	$P\bar{v}_{CO_2}$ (kPa)	$C\bar{v}_{O_2}$ (ml dl^{-1})
1	34.7	3.92	1	9.8	3.31	5.24	6.2
1	41	6.47	1	11	4.31	4.76	9.2
1	44.7	7.64	1	11.1	6.40	4.95	12.2
1	43.1	5.88	1	9	4.60	4.51	8.3
1	46.2	7.25	1	11.1	5.11	5.23	11.1
1	48.5	5.88	1	11.5	5.11	5.83	11.2
2	55.6	11.21	1	10.2	7.00	7.55	11.3
2	32.3	7.65	0.8	9.8	5.71	6.80	10.8
2	40.1	7.65	0.75	11	4.91	6.25	9.9
2	37.7	9.61	0.75	9.1	5.91	6.45	9.4
2	38.9	8.54	0.7	8.6	5.80	7.05	9
3	34.5	10.01	1	9.3	5.80	4.44	10.5
3	33.5	10.01	1	7.9	5.60	5.80	7.9
3	34.1	8.74	0.9	11.7	5.71	6.27	12.2
3	44.8	10.56	1	10.5	5.20	7.04	10.4
3	28.6	11.10	0.8	10.5	6.31	5.91	11.5
4	52	18.66	0.7	13.2	8.00	7.51	16.1
4	52.5	15.49	1	13.4	8.71	10.23	16.8
4	30	13.02	0.8	11.2	6.11	6.23	12.9
4	40.9	17.25	1	12.1	6.60	7.83	14.1
4	52.6	18.48	0.8	10.6	7.11	7.61	13
5	33.1	9.37	1	10.4	3.40	8.20	10.2
5	35.8	8.47	1	10.7	5.60	7.55	10.9
5	37.5	9.81	0.9	10.1	5.91	7.57	10.3
5	32	9.37	0.8	10.8	5.40	7.91	10.4
5	40.8	10.04	0.9	9.4	6.00	8.11	9.7
5	47	10.04	1	9.4	5.00	8.91	9.1
6	45.4	12.35	1	11.7	5.40	5.39	11.5
6	38.2	8.43	1	12.2	5.20	5.11	12.4
6	37.2	8.43	1	12.2	4.80	5.60	11.7
6	38.1	10.58	1	11.4	5.51	5.85	11.6
7	34.2	9.20	0.9	10.9	6.11	8.71	11.8
7	36.1	8.00	1	11.3	6.11	8.11	12.6
7	40.1	11.80	0.8	10.8	6.31	6.60	12.5
7	48.8	11.10	0.8	11.4	6.40	7.40	13
7	33.4	12.70	0.7	9.5	6.31	7.31	10.7
7	34.3	12.30	0.8	11	5.91	7.51	11.4
8	47	8.00	1	10.7	6.51	6.91	12.2
8	37.3	8.00	0.7	7.8	5.80	7.20	8.8
8	39.8	9.70	0.7	9.7	5.51	8.71	9.8
8	31.7	7.20	0.9	10.8	5.11	7.40	10.2
8	41.4	7.90	1	10.4	5.60	8.91	10.6
8	42.1	8.30	0.9	10	6.20	7.80	11.3
9	55.6	9.20	1	11.5	5.20	6.51	12.1
9	42.8	6.20	1	13.3	5.00	5.00	13.8
9	45.5	10.20	0.95	12.6	6.11	6.60	14.1
9	54.6	11.70	0.9	12.4	6.51	7.51	13.9
9	46	9.50	0.95	12.2	5.51	5.47	13.6
9	47.9	9.00	0.95	12.2	4.91	5.20	13
9	37.3	9.00	0.9	10.8	4.91	5.24	11
10	44.1	8.60	0.8	12.4	7.91	7.31	16
10	22.9	6.30	0.6	13.2	5.80	6.51	15.1
10	22.6	5.60	0.5	11.5	6.40	6.35	13.4
10	20.9	5.60	0.5	11.8	5.80	6.47	12.9
10	26.3	6.40	0.6	11.5	6.0	6.60	13.1

$$So_2 = \frac{Po_2^{\,n}}{Po_2^{\,n} + P_{50}^{\,n}} \times 100 \qquad (2)$$

(where So_2 is the haemoglobin oxygen saturation (%) and Po_2 is the partial pressure of oxygen in the blood). Reference values of n=2.7 and P_{50}=3.576 kPa (26.8 mm Hg) were used, based on the work of Siggard-Anderson.[35 36]

The alveolar oxygen tension PA_{O_2} in each of the compartments for the respiratory exchange ratio (R) associated with each $\dot{V}A/\dot{Q}C$ and PA_{CO_2} was calculated from the alveolar gas equation:[32]

Table 2 Measured Pa_{O_2} and Pa_{O_2} predicted from ARDS lung model (kPa)

Patient	Measured Pa_{O_2}	Predicted Pa_{O_2}
1	7.51	7.81
1	7.51	8.09
1	13.31	11.28
1	8.60	9.11
1	8.80	9.01
1	8.20	8.24
2	10.91	9.37
2	14.71	15.72
2	8.60	8.13
2	11.80	10.64
2	11.20	10.40
3	25.30	19.86
3	22.10	19.86
3	13.91	12.20
3	9.20	9.27
3	20.50	17.76
4	12.80	10.89
4	15.40	14.57
4	26.80	19.86
4	16.40	15.11
4	16.31	11.95
5	13.60	12.79
5	15.31	12.48
5	15.51	11.17
5	11.51	10.72
5	11.60	10.72
5	8.80	8.83
6	9.11	8.83
6	11.20	10.80
6	9.31	10.04
6	11.60	11.08
7	14.60	14.09
7	17.91	16.44
7	13.51	12.95
7	9.91	10.11
7	15.31	13.88
7	11.40	11.37
8	12.60	11.95
8	13.71	13.29
8	9.80	9.37
8	11.40	11.37
8	10.71	10.64
8	12.71	12.79
9	7.91	8.31
9	9.20	9.77
9	10.80	10.80
9	9.40	9.11
9	9.60	10.64
9	7.80	9.37
9	9.80	10.89
10	25.50	19.86
10	19.90	16.05
10	17.40	15.40
10	14.11	13.68
10	14.51	14.57

$$PA_{O_2} = 713 \times FI_{O_2} - PA_{CO_2}[FI_{O_2} + (1 - FI_{O_2})/R] \quad (3)$$

In deriving the oxygen saturation of end-capillary blood, the transformation described by Kelman[37] was used to calculate a value of P_{50} (P'_{50}) for the oxygen dissociation curve to account for different values of saturation and partial pressure of carbon dioxide in the blood (Pc_{O_2}) from the equation:

$$P'_{50} = P_{50} \times 10^{-[0.4(\mathrm{pH}-7.4)+0.06(\ln 40-\ln Pco_2)]} \quad (4)$$

where pH is calculated from the equation:

$$\mathrm{pH}=7.59+0.0031\times \mathrm{Hb}(1-\mathrm{So}_2)-0.2741\times \ln(\mathrm{PCO}/20) \quad (5)$$

The shape of the curve was assumed to be invariant under this translation and the effects of pH caused by metabolic changes, temperature and 2,3-DPG were omitted from the equation. Similar Kelman transformations for the CO_2 dissociation curves were carried out for each alveolar compartment.[31] Because oxygen saturation is not known, it was calculated, for each alveolar compartment, by an iterative process designed to terminate when the values of oxygen content, carbon dioxide content, P_{CO_2}, P_{O_2} and oxygen saturation satisfy both the oxygen and carbon dioxide dissociation curves.

Distribution of lung compartments in the model

For each lung compartment, alveolar ventilation may be described by the logarithmic normal distribution function[31] multiplied by a scaling constant:

$$f(x) = k\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2} \quad (6)$$

(where $f(x)=\dot{V}\mathrm{A}$, $x=\ln(\dot{V}\mathrm{A}/\dot{Q}\mathrm{C})$, μ is the log mean value and σ is the log standard deviation of the ventilation/perfusion distribution with scaling constant k).

Based on the data provided by Dantzker *et al.*,[12] the following values were used to describe the ARDS lung: $\sigma=0.43$, $\mu=2.921$ and $k=2.13$. Alveolar ventilation of 9.28 litres (dead space 3.75 litres) and cardiac output of 6.65 litres (shunt 2.71 litres) were derived from Dantzker *et al.*[12] Following Lee *et al.*,[15] the lung compartments were spaced evenly on a logarithmic scale of 0.1 $\log_{10}$ units from −2 to +2, which covers the range of $\dot{V}\mathrm{A}/\dot{Q}\mathrm{C}$ from 0.01 to 100 in 41 compartments. Shunt and dead space were included as two separate compartments, resulting in a total of 43 compartments in the entire model. Because for each compartment the ventilation $\dot{V}\mathrm{A}$ is known and $\dot{V}\mathrm{A}/\dot{Q}\mathrm{C}$ is known, the corresponding $\dot{Q}\mathrm{C}$ may be derived from equation 6. Thus, the weighted sum of the end-capillary oxygen concentration for each lung compartment with the associated $\dot{V}\mathrm{A}/\dot{Q}\mathrm{C}$, R, PA_{CO_2}, PA_{O_2} and Cc'_{O_2} from all the compartments accounts for the gas exchange from the entire lung model.

Appendix 2. Data used to validate ARDS lung model

Data used to validate the ARDS lung model are given in Table 1.

Measured Pa_{O_2} and Pa_{O_2} predicted from ARDS lung model (kPa) are shown in Table 2.

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Estimation of changes in cardiac output from the arterial blood pressure waveform in the upper limb[†,††]

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We have developed a new pulse contour cardiac output (PulseCO) algorithm based on frequency analysis studies of the arterial system. PulseCO was compared with thermodilution cardiac output (TDCO) in 10 patients undergoing cardiac surgery. Results from one patient were unsuitable for analysis. In the remaining nine patients, 142 TDCO determinations were compared with PulseCO after logarithmic transformation and after being normalized by the initial cardiac output in each patient. Each determination was usually the average of three measurements. Least squares regression gave y=0.77x (r^2=0.81) and the limits of agreement were from −26% to +21%. The accuracy of PulseCO in determining short-term changes in cardiac output was assessed by comparing the ratios of consecutive PulseCO determinations with the ratios of the corresponding, consecutive TDCO determinations. Least squares regression gave y=0.71x (r^2=0.70) and the limits of agreement were from −21% to +25%. After phenylephrine had been given to five patients, PulseCO showed an increase in systemic vascular resistance consistent with the known pharmacological actions of the drug. The PulseCO algorithm was incorporated into a computer program that acquires arterial pressure data from an analogue-to-digital converter and displays beat-to-beat trend values.

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The concept that the arterial pulse contour might be used to infer cardiac output (CO) goes back to at least 1904.[1] In 1970, Kouchoukos and colleagues[2] investigated a 'systolic area' pulse contour method to estimate stroke volume from the area under the systolic part of the arterial pressure waveform. Since then, a number of other researchers have pursued this approach by adding various correction factors[3–5] and a three-element Windkessel model has also been used to derive CO.[6 7] In humans, these methods have not been shown to be accurate when there are large changes in haemodynamic state; for example, errors have been reported with changes in systemic vascular resistance (SVR).[7 8]

The arterial blood pressure waveform measured in a peripheral artery arises from the interaction between the arterial system and the heart. Left ventricular ejection creates a wave that travels (usually at 6–10 m s^{-1}) through the arteries and is reflected from the periphery. At any point in the arterial system, a measured waveform may be decomposed into its forward and backward components. In the aorta, viscous effects are negligible so that components of flow and pressure travelling in the same direction are similar in shape. Theoretically, if wave reflection were absent, then the pressure and flow contours in the aorta would be identical, their magnitudes being related by the aortic characteristic impedance. Differences between the pressure and flow contours in the aorta occur because backward waves result in augmentation of the pressure but retardation of the flow.

The relationship between the forward and backward waves can vary considerably. For example, if the SVR decreases, reflection at the arterial–arteriolar junctions will lessen, reducing the backward wave in the aorta.[9] Small doses of nitroglycerine cause arterial dilatation, which can reduce wave reflection with minimal changes in SVR and in the mechanical properties of the aorta.[10 11] The mechanical properties of the aorta and other large arteries govern the pulse wave velocity and consequently the timing of wave reflection.

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The aortic pressure waveform is governed by the relationship between pressure and flow in the aorta (aortic input impedance) and also by the aortic flow itself. Normally, the ventricle acts neither as a pure 'pressure source' nor as a pure 'flow source',[12] wave reflection augmenting aortic pressure and retarding flow. However, in heart failure the ventricle acts as a 'pressure source' and reflected waves returning before aortic valve closure do not significantly augment the pressure because the ventricle cannot generate the required increase in wall tension. Instead the reflected wave has a greater effect upon the flow, which is significantly retarded, and pressure augmentation is only observed once the aortic valve has closed.

Pulse contour methods must attempt to track changes in CO and SVR despite changes in ventricular ejection and in wave reflection. Previous approaches to pulse contour analysis have been justified theoretically by simple models[2 6 13] but these do not account for wave travel. However, frequency analysis has been widely used to characterize the arterial system.[14] There are many studies in which aortic input impedance has been calculated, *in vivo* and in computer simulations, and used to interpret ventricular–vascular interaction. The relationship between forward and backward waves can be quantified precisely by aortic input impedance in the frequency domain and the relationship between aortic pressure and radial artery pressure has also been investigated with similar mathematical techniques.

The aim of this study was to develop a new pulse contour CO algorithm with a direct link to recent frequency analysis studies of the arterial system and to design a robust algorithm that was more accurate than existing pulse contour methods. The algorithm was assessed by comparison with thermodilution cardiac output (TDCO) measurements in 10 patients undergoing cardiac surgery.

Patients and methods

New pulse contour algorithm

Notation

The following abbreviations are used below: $|X|_1$, the modulus of X at the frequency of the first harmonic; Z_{AII}, aortic input impedance; T_{A-RA}, aorta to radial artery transfer function. Throughout this report, 'aortic flow' refers to the velocity of blood and impedance refers to the relationship between pressure and velocity, as recommended by Nichols and O'Rourke for studies of vascular impedance.[14] All equations presented below and in the appendix are intended to be used in the range 0.5–2.0 Hz (30–120 min^{-1}).

General approach

The algorithm is based upon the first harmonic of the arterial pressure waveform. In relating the first harmonic of the arterial pressure to CO, a series of approximations is made. These include the relationship between |radial artery pressure|$_1$ and |aortic pressure|$_1$; the relationship between |aortic pressure|$_1$ and |aortic flow|$_1$; and the relationship between |aortic flow|$_1$ and CO. This can be stated mathematically as

$$\mathrm{CO} = \left\{ \frac{\mathrm{CO}}{|\,\text{aortic flow}\,|_1} \times \frac{|\,\text{aortic flow}\,|_1}{|\,\text{aortic pressure}\,|_1} \times \frac{|\,\text{aortic pressure}\,|_1}{|\,\text{radial pressure}\,|_1} \right\} \times |\,\text{radial pressure}\,|_1 \qquad [1]$$

This can be restated as:

$$\mathrm{CO} = \left\{ \frac{\mathrm{CO}}{|\,\text{aortic flow}\,|_1} \times \frac{1}{|\,Z_{AII}\,|_1} \times \frac{1}{|\,T_{A-RA}\,|_1} \right\} \times |\,\text{radial pressure}\,|_1 \qquad [2]$$

The approximations for (CO/|aortic flow|$_1$), $|Z_{AII}|_1$ and $|T_{A-RA}|_1$ are presented in the Appendix. CO is calculated each beat from the beat duration, ejection duration, mean arterial pressure (MAP) and the modulus and phase of the first harmonic of the waveform. (The age and sex of the subject are also used in the calculation.) The algorithm calculates relative changes in CO and requires calibration so that absolute values can be displayed.

Arterial pressure processing

The radial (or brachial) arterial pressure recording concurrent with each TDCO measurement was converted to digital form and stored. A program written with Matlab (MathWorks, Inc.) was used to analyse the arterial pressure traces using the equations described in the Appendix. Microsoft Excel (Microsoft Corporation) was used to perform statistical analysis of the results. The equations were also implemented using C (Symantec C/C++; Symantec Corporation) to verify the Matlab code and to ensure that the algorithm could display the information effectively on a beat-by-beat basis in 'real time', whilst acquiring data from an analogue-to-digital converter.

Patients

Study subjects

Ten patients were studied during cardiac surgery. No patient had known aortic valve incompetence and all gave written informed consent to be included in the study, which was approved by St Thomas' Hospital Research Ethics Committee.

Protocol

After induction of anaesthesia, a thermodilution pulmonary artery catheter sheath was placed in the right internal jugular vein. An arterial cannula (20- or 18-gauge) was inserted into a radial or brachial artery, according to the usual practice of the anaesthetist. Anaesthesia was maintained with isoflurane.

We used a monitor with an analogue output card (Hewlett Packard, Andover, MA, USA) so that the blood pressure could be recorded on tape (R-61 or RD-130T; Teac Corporation, Tokyo, Japan). A Baxter 150 cm pressure tube connection and Baxter Truwave PX-600F transducer (Baxter Edwards Critical-Care, Irvine, CA, USA) were used to measure arterial pressure. A 'pop-test'[14] showed that these had a flat (±5%) frequency response up to 2.25 Hz (natural frequency 9.8 Hz, damping ratio 0.24). Once monitoring of the patient in the operating theatre had started, a thermodilution pulmonary artery catheter (Baxter Edwards Critical-Care or Abbott Laboratories, North Chicago, IL, USA) was advanced through the right atrium and right ventricle into the pulmonary artery so that a wedge pressure was achieved with a balloon inflation of 1–1.5 ml air. When the position of the catheter was satisfactory, CO measurements were started.

We took an opportunistic approach to TDCO measurements to maximize the information about CO obtained from the pulmonary artery catheter. Dextrose (10 ml, at room temperature) was used as the injectate and a thermistor on the injection port was used to measure the injectate temperature. If possible, groups of three measurements were made whenever the state of the patient changed or at least every 10 min. TDCO measurements were not attempted when there were gross dysrhythmias (this only affected the pre-bypass period of patient 2) and more than three measurements per group were made if there appeared to be excessive variability. Each measurement was made during a brief period of apnoea and fast running infusions were halted to improve accuracy.[15] PulseCO was derived from the arterial pressure recording concurrent with each TDCO measurement.

In a further group of five patients, the response to a low dose (0.25 mg or 0.5 mg) bolus injection of phenylephrine was investigated using PulseCO. Written informed consent was obtained and the study was approved by St Thomas' Hospital Research Ethics Committee.

Statistical evaluation

For each patient, individual measurements of TDCO and PulseCO were plotted against time. The SVR derived from each TDCO and PulseCO value was also plotted because of reports that existing pulse contour algorithms are inaccurate when there are changes in SVR.[7] The calibration factor was chosen so that the first TDCO and PulseCO determinations were the same in each patient.

For the remaining analysis, TDCO outliers were identified from the graphs of TDCO against time and excluded (3.8% of the TDCO measurements were rejected—see Figure 1). If there was only one remaining TDCO measurement in a group, the entire group was excluded from further analysis. The TDCO and PulseCO measurements in each group were then averaged (the averaged values of a group will be referred to as a determination).

Pulse contour CO methods are intended to track changes in a patient's CO after calibration (using a dilution technique) in that individual. It is misleading to pool the calibrated results from a number of patients with different COs because the range of the pooled, calibrated COs may be much greater than the CO range in any individual patient. A correlation with the dilution technique is then inevitable, as a result of the calibrations, even if the ability of the method to track changes in an individual patient is poor. The statistical evaluation performed here attempts to overcome this problem.

For each method, the first CO determination in each patient was used to normalize the CO determinations from that individual. For the remaining determinations, ($\text{PulseCO}/\text{PulsoCO}_{\text{start}}$) was compared with ($\text{TDCO}/\text{TDCO}_{\text{start}}$) (where the subscript 'start' refers to the first determination in that patient). This comparison tests the ability of PulseCO to estimate the 'within-patient change' in CO, expressed as a percentage of the starting CO. The method of analysis described by Bland and Altman[16] was used for the comparison, including logarithmic transformation of the data. Bland and Altman provide a worked example of such an analysis. The intercept of the regression line was set to zero so that the regression line passed through the 'start' values.

In order to investigate further the ability of PulseCO to track short-term changes in CO, the ratio of consecutive PulseCO determinations was compared with the ratio of the corresponding, consecutive TDCO determinations. Thus, ($\text{PulseCO}_{i+1}/\text{PulseCO}_i$) was compared with ($\text{TDCO}_{i+1}/\text{TDCO}_i$), where i corresponds to the determination number. Again, the method of analysis described by Bland and Altman[16] was used. The comparison of consecutive ratios is not statistically independent of the comparison of within-patient change (for example, a perfect agreement in one implies perfect agreement in the other). However, both tests were performed in order to give an indication of long-term as well as short-term accuracy.

Results

All 10 patients (nine males and one female) had coronary artery bypass grafts and patient 2 also had a mitral valve replacement. In patient 2, the number of determinations obtained before cardiopulmonary bypass was limited by dysrhythmias (see Patients and methods) and the dicrotic notch could not be detected in any of the post-bypass pressure waveforms (see Figure 2), so this patient was excluded from further analysis. In the other nine patients, the dicrotic notch was identified reliably from the arterial pressure waveform corresponding to all but five of the remaining 494 TDCO measurements (these five were also excluded). The arterial pressure recording corresponding to one TDCO measurement was rejected because the waveform was damped.

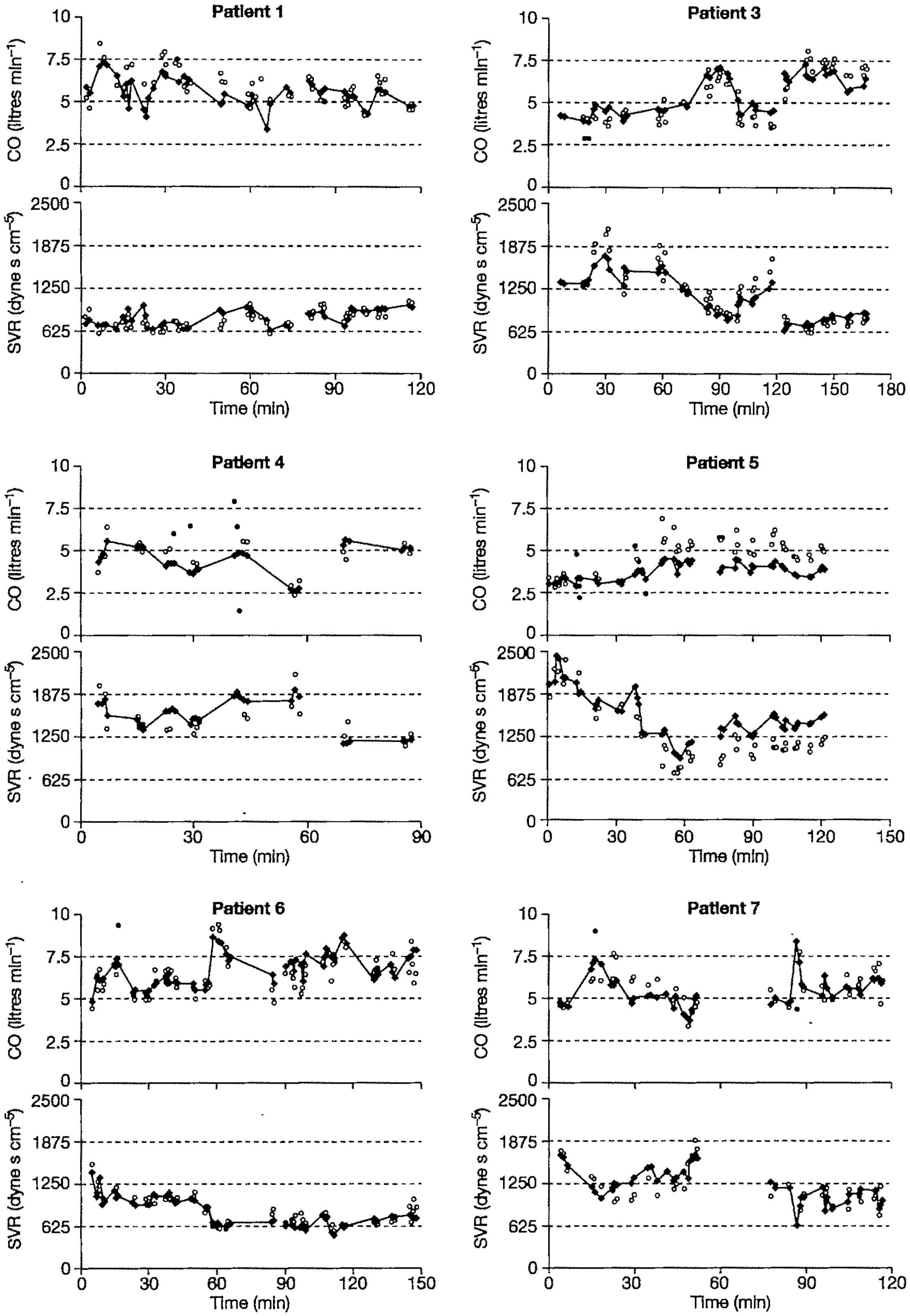

Fig 1 Trend plots for cardiac output (CO) and systemic vascular resistance (SVR) in each patient. See p. 490 for details.

Figure 1 shows the trend plots for CO and SVR in each patient. Every TDCO measurement and corresponding PulseCO value is indicated on these graphs; they allow qualitative interpretation of the raw data. Nineteen of the 494 TDCO measurements (3.8%) were rejected because the TDCO values were incompatible with the patient's haemodynamic state (see Figure 1). For example, in patient 4, the three TDCO measurements at 40 min varied from 1.5 to 7.9 litres min^{-1} despite a stable arterial pressure and heart rate. The remaining TDCO measurements were used to obtain 151 TDCO determinations (on average, there were 3.06 measurements per determination).

Table 1 shows the age, height, weight and the ranges of MAP, TDCO and SVR values in each patient (SVR being calculated from MAP and TDCO). Figure 3 shows the Bland–Altman analysis for the within-patient change estimated by each method (($\text{PulseCO}/\text{PulseCO}_{\text{start}}$) against ($\text{TDCO}/\text{TDCO}_{\text{start}}$)). Log-transformed data were used for the analysis.[16] The axes are labelled with the corresponding back-transformed values for ease of interpretation. Figure 4 shows a similar comparison of the ratios of consecutive determinations (($\text{PulseCO}_{i+1}/\text{PulseCO}_i$) against ($\text{TDCO}_{i+1}/\text{TDCO}_i$)).

The data were reanalysed with inclusion of the 19 TDCO measurements that were rejected (see above). The limits of agreement for the comparison of ($\text{CO}/\text{CO}_{\text{start}}$) were −27% to +21% (previously −26% to +21% (Figure 3)). The limits of agreement for ($\text{CO}_{i+1}/\text{CO}_i$) were −21% to +26% (previously −21% to +25% (Figure 4)). The lack of impact of the excluded thermodilution measurements upon the limits of

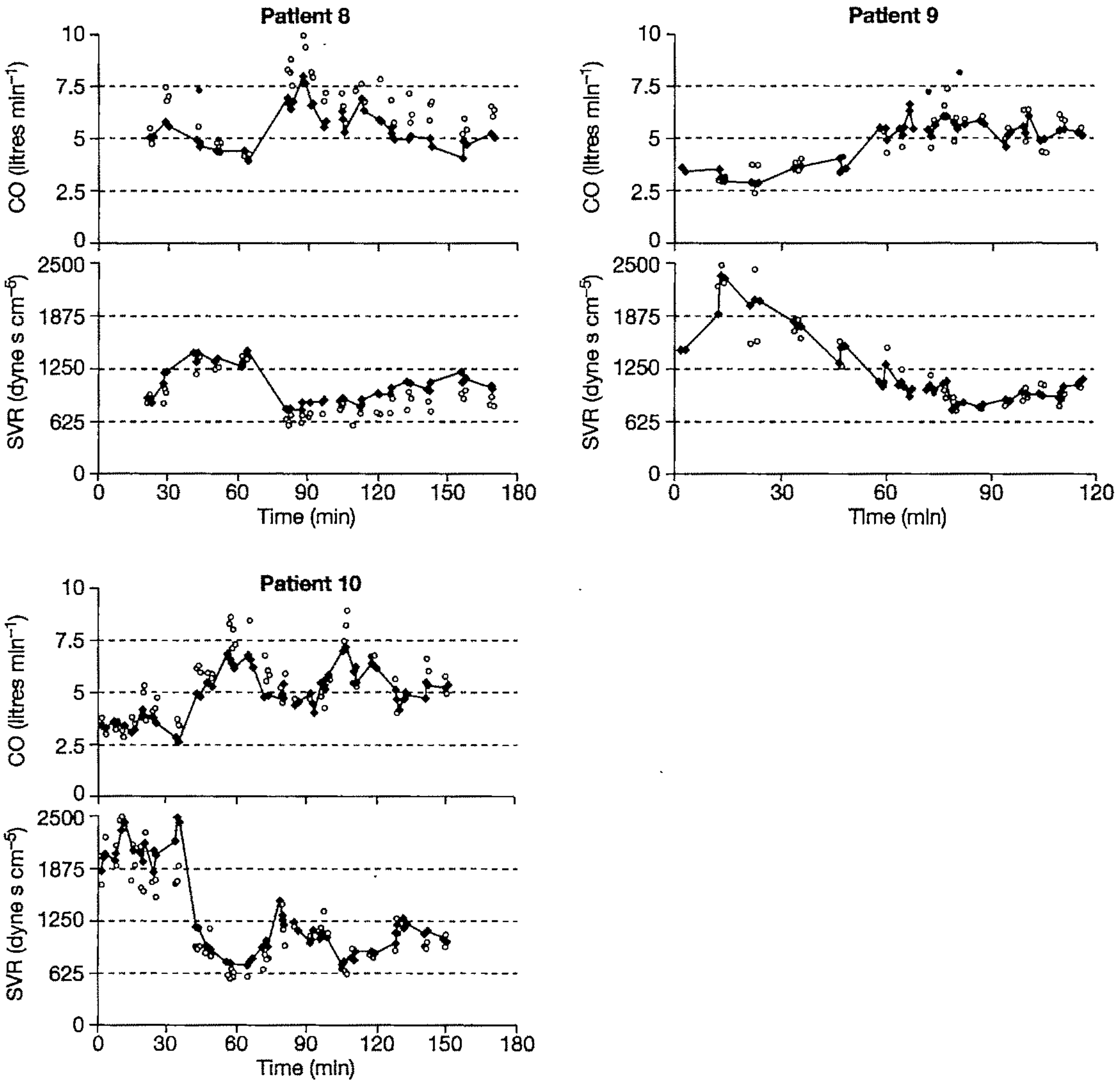

Fig 1 (continued) Trend plots for cardiac output (CO) and systemic vascular resistance (SVR) in each patient. CO and SVR obtained using thermodilution are plotted with open circles. Filled circles indicate thermodilution measurements that were rejected. The diamonds connected by a solid line represent CO and SVR values obtained with PulseCO. The calibration factor was chosen so that the first PulseCO and TDCO determinations were the same in each patient. Patient 2 is not shown (see text). Cardiopulmonary bypass is indicated by a break in the line joining the PulseCO values (the duration of bypass has been omitted).

agreement was a result of the small number of measurements that were rejected.

The standard error of TDCO measurements, assessed using one-way analysis of variance, was 9%. On average, there were 3.06 measurements per determination, so the expected error for each determination (precision) was $9/\sqrt{3.06} = 5\%$ (assuming a bias of zero).

In the five patients in whom the response to a bolus injection of phenylephrine was measured, the changes in SVR and CO between the time of injection and the time of the initial peak in MAP were recorded. On average, MAP increased from 71 (SD 9) mm Hg to 95 (SD 14) mm Hg. PulseCO indicated an associated increase in SVR by 59 (SD 35) % with a small fall in CO (4.4 (SD 1.4) litres min^{-1} to 3.8 (SD 1.5) litres min^{-1}).

Discussion

We have used the first harmonic of the arterial pressure waveform as the basis of a new algorithm for deriving CO. This was done because the pressure measurement systems used in the clinical setting have a poor frequency response and because aortic input impedance and the aorta–radial artery pressure transfer function are both more predictable at low frequencies. To develop an equation for predicting aortic input impedance, we used results from an anatomically and physiologically realistic model of the arterial system[17 18] in conjunction with equations to estimate the elastic properties of the aorta from MAP (as well as the patient's age and sex).[19 20] The ejection duration (relative to the total cycle duration) and the phase of the first harmonic of the radial artery pressure are used to distinguish between changes in ventricular ejection and changes in wave reflection (see Appendix).

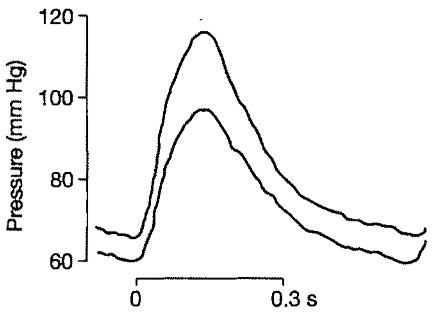

Fig 2 Arterial pressure waveforms from patient 2. The position of the dicrotic notch could not be found.

There are circumstances when the assumptions made in developing the algorithm will not be met. In any particular patient, it is assumed that the pulse wave velocity and changes in aortic cross-sectional area are only dependent upon MAP. Drugs that affect smooth muscle tone can alter the properties of the aorta independently of pressure, although the extent of this effect is small relative to the other effects that are induced.[10 11] These changes to the mechanical properties of the aorta are associated with changes in wave reflection caused by alterations to smooth muscle tone in the muscular arteries. Hence, the effects might be predictable from changes in the estimated phase of the aortic input impedance.

To estimate the first harmonic of the aortic pressure, the pressure transfer function from the aorta to radial artery is assumed to be constant (i.e. a function of frequency alone). Radial artery pressure is usually reliable. However, it is well known that radial artery pressure can occasionally become unrepresentative of a patient's central haemodynamics. This can occur during high-dose vasopressor therapy[21] and after cardiopulmonary bypass.[22] If the gross features of the arterial waveform become severely distorted, the waveform is unsuitable for analysis and any estimation of CO will become unreliable.

The algorithm may be inaccurate when there are marked changes in the ejection profile relative to the ejection duration (see Appendix). In particular, the flow patterns sometimes observed in hypertrophic cardiomyopathy[14] could result in large errors. In patients with aortic incompetence, flow through the aortic valve will not be zero

Table 1 Age, height, weight and ranges of mean arterial pressure, cardiac output and systemic vascular resistance in each patient. MAP, mean arterial pressure; TDCO, thermodilution cardiac output; SVR, systemic vascular resistance. Minimum and maximum values refer to determinations (rather than individual measurements)

Patient	Age (yr)	Height (m)	Weight (kg)	MAP (mm Hg)		TDCO (litres min^{-1})		SVR (dyne s cm^{-5})	
				min	max	min	max	min	max
1	67	1.55	79	49	66	4.3	7.7	640	1010
2	61	1.79	85	51	86	3.2	7.6	770	1750
3	70	1.65	77	56	96	3.6	7.5	630	2000
4	65	1.78	80	63	106	2.8	5.5	1200	1800
5	75	1.65	74	52	89	3.1	6.0	770	2200
6	72	1.80	88	47	99	5.0	9.1	560	1200
7	63	1.79	98	69	103	4.1	7.1	950	1700
8	59	1.81	97	57	85	4.3	9.7	640	1400
9	74	1.86	96	56	88	3.0	7.0	800	2300
10	64	1.80	83	58	104	3.2	8.2	610	2590

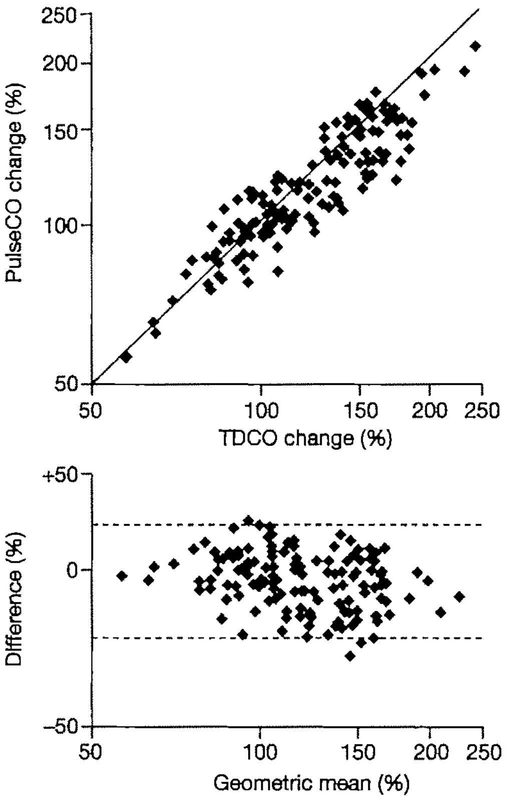

Fig 3 Bland–Altman analysis for the within-patient change estimated by each method (*n*=142). PulseCO change is calculated as PulseCO/PulseCO$_{start}$ and TDCO change as TDCO/TDCO$_{start}$, where 'start' refers to the first determination in that patient (see Patients and methods). The line of identity is shown and the limits of agreement are marked on the Bland–Altman plots beneath. Least squares regression gave y=0.77x, r^2=0.81 (95% confidence interval 0.75–0.86) and the limits of agreement were from –26% to +21%.

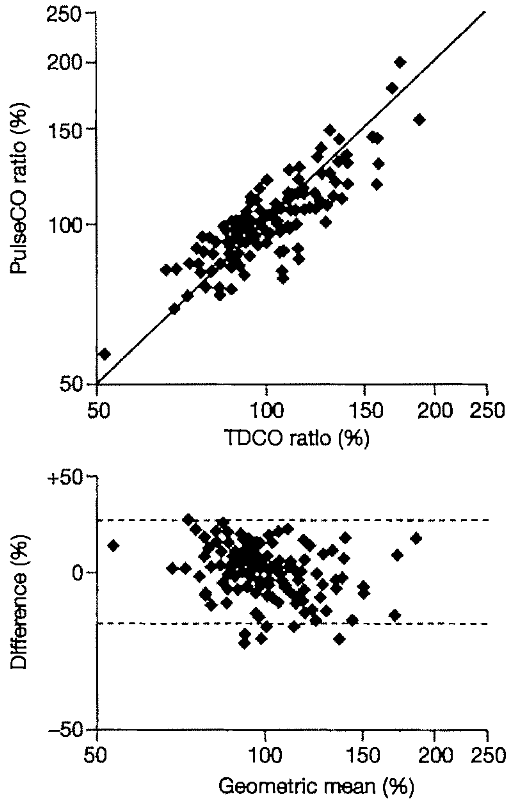

Fig 4 Bland–Altman analysis for the ratios of consecutive determinations estimated by each method (PulseCO$_{i+1}$/PulseCO$_i$ against TDCO$_{i+1}$/TDCO$_i$) (*n*=142). The line of identity is shown and the limits of agreement are marked on the Bland–Altman plots beneath. Least squares regression gave y=0.71x, r^2=0.70 (95% confidence interval 0.61–0.77) and the limits of agreement were from –21% to +25%.

during diastole, as was assumed for the development of the algorithm. We are developing a method to detect conditions when the arterial pressure waveform is unsuitable for analysis or when recalibration should be performed.

Bolus thermodilution was used to measure CO for the comparison with pulse contour analysis because it is the most commonly used method and because measurements can be made in rapid succession. However, it does not provide an unequivocally correct measurement. In this study, steps were taken to minimize thermodilution inaccuracies (see Patients and methods); the precision of TDCO measurements in this paper is close to the value obtained by other investigators in non-surgical critical care settings.[23] Nevertheless, the calculated error for each TDCO determination was 5% and this contributed to the differences between PulseCO and TDCO.

Pulse contour methods for calculating CO require calibration using another method. Thermodilution or the less invasive lithium dilution method[24] could be used for this purpose. The limits of agreement between PulseCO and TDCO indicate that clinically significant differences can occur between the methods. For this reason, we suggest that before major clinical decisions are taken, the calibration should be checked. The need to recalibrate could be triggered by the PulseCO algorithm when large changes to the predicted aortic input impedance have occurred. In particular, the agreement between PulseCO and TDCO would have improved if recalibration had been performed in patients 5 and 8 (Figure 1).

A pulse contour algorithm based upon the three-element Windkessel model has previously been compared with thermodilution in eight cardiac surgical patients.[6] The limits of agreement between pulse contour CO and quadruple thermodilution determinations were –14% to +18% (mean±2SD) once a calibration had been performed before induction of anaesthesia. However, the range (minimum—maximum) of CO was small (mean range 2.2 litres min^{-1}) compared with the present study (mean range 3.9 litres min^{-1}) and there were fewer TDCO determinations per patient.

There are several possible reasons why this algorithm may be more accurate than the pulse contour method based upon the three-element Windkessel model. First, our algorithm incorporates a model of the pressure transfer from the aorta to the radial artery, whereas radial pressure is

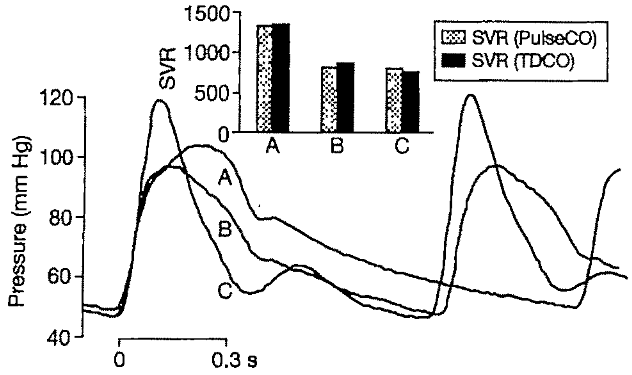

Fig 5 Arterial pressure waveforms from patient 3 with similar mean values. In this patient, a marked decrease in systemic vascular resistance (SVR) (and in the magnitude of wave reflection) occurred during the operation but this was not associated with a change in MAP. Values of SVR (dyne s cm^{-5})) are indicated, as assessed by TDCO and PulseCO. Traces A, B and C correspond to determinations at 7, 95 and 145 min, respectively (see Figure 1).

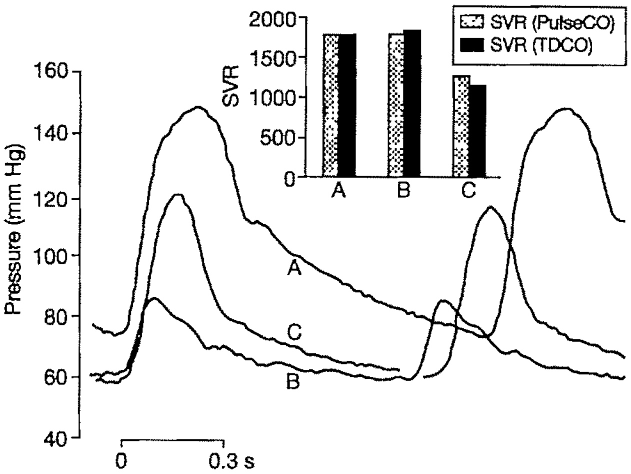

Fig 6 Arterial pressure waveforms from patient 4 with a wide range of MAP. Trace A occurred after skin incision. Before cardiopulmonary bypass, the patient became hypotensive (B) and the algorithm correctly indicated that this was not due to a fall in systemic vascular resistance. After cardiopulmonary bypass, systemic vascular resistance was lower (C). Values of systemic vascular resistance (SVR; in dyne s cm^{-5}) are indicated, as assessed by TDCO and PulseCO. Traces A, B and C correspond to determinations at 6, 57 and 71 min, respectively (see Figure 1).

assumed to be equal to aortic pressure in the three-element Windkessel method. Second, our algorithm uses a model of the arterial system in which wave reflection is well represented, whereas in the three-element Windkessel model, wave travel phenomena are not characterized. In a previous study, the three-element Windkessel model reproduced the gross features of aortic input impedance in dogs, but invasive aortic flow measurements were used to optimize the parameters of the model.[25] Therefore, that study has limited applicability to pulse contour analysis because these flow measurements are not available in patients.

A version of the three-element Windkessel algorithm has been investigated, that has been modified by a correction factor to reduce the effects of MAP upon arterial impedance; details of this modification have not been published.[7] The algorithm can be inaccurate when there are changes in SVR.[7] In 10 patients the device was recalibrated after cardiac surgery and then a phenylephrine infusion was administered for 20 min. On average, the initial CO was 6.1 litres min^{-1} and bolus thermodilution showed no significant change at the end of the infusion (average thermodilution was then 5.7 litres min^{-1}); the MAP increased because of a 62 (SD 29)% increase in SVR. However, the modified three-element Windkessel algorithm indicated an average increase in CO of 3.2 litres min^{-1} ($P<0.05$) and so the increase in SVR induced by the infusion was seriously underestimated. Applying the pulse contour algorithm to femoral artery pressure may have exacerbated these errors because the relationship between femoral artery pressure and aortic pressure would be expected to change with changes in the reflection coefficient of vascular beds in the trunk (see Appendix).

When we assessed the response to a bolus injection of phenylephrine, the PulseCO algorithm indicated a 59% increase in SVR and a small decrease in CO. This response is consistent with the changes determined by Rödig and colleagues[7] using thermodilution, after the administration of a phenylephrine infusion. PulseCO was also accurate in conditions when the SVR changed but the MAP remained the same (Figure 5) as well as conditions when the changes in SVR were small relative to changes in MAP (Figure 6).

The PulseCO algorithm estimates changes in CO and SVR with an immediate response time and is likely to be more accurate than clinical estimations of such changes. Other methods for determining CO continuously are available. For example, continuous thermodilution has been assessed recently,[26 27] with the authors concluding that it is reliable enough for clinical use. However, the response time to changes in CO is slow (minutes), the device is unreliable during rapid infusion of fluids, and pulmonary artery catheterization is required. PulseCO may be useful in the management of unstable patients when rapid haemodynamic changes are occurring or when treatment is being adjusted. It may also be useful in stable patients for detecting changes that might otherwise have gone unnoticed, such as a progressive decrease in CO compensated by an increase in SVR.

The algorithm was successfully incorporated into a computer program written in C. This allows the arterial pressure data to be analysed whilst it is being acquired with an analogue-to-digital converter. Optimal display of the information obtained from the PulseCO algorithm can maximize the clinical usefulness of the method. The display has trend plots that show beat-by-beat changes with an immediate response time and can follow the effect of interventions such as giving vasoactive drugs.

This study has shown that the PulseCO algorithm has advantages over other pulse contour methods and can estimate CO continuously and simply from a minimally invasive measurement.

Appendix

Details of the new pulse contour algorithm

Below, $|X|_1$ and $\phi(X)_1$ are the modulus and phase of X at the frequency of the first harmonic (if the subscript '1' is omitted, the description is valid for any frequency). A is the cross-sectional area of the aorta, v is the pulse wave velocity in the thoracic aorta (m s^{-1}) and f is the frequency (Hz). Other abbreviations are defined in the text. Throughout this report, 'aortic flow' refers to the velocity of blood and 'impedance' refers to the relationship between pressure and velocity, as recommended by Nichols and O'Rourke for studies of vascular impedance.[14] All equations presented below are intended to be used in the range 0.5–2.0 Hz (30–120 min^{-1}).

Approximations for (CO/|aortic flow|$_1$), $|Z_{\text{AII}}|_1$ and $|T_{\text{A-RA}}|_1$ are required:

$$\text{CO} = \left\{ \frac{\text{CO}}{|\text{ aortic flow }|_1} \times \frac{1}{|\,Z_{\text{AII}}\,|_1} \times \frac{1}{|\,T_{\text{A-RA}}\,|_1} \right\} \times |\text{ radial pressure }|_1 \qquad [2]$$

Aortic input impedance (Z_{AII})

Karamanoglu and colleagues[17] described a model consisting of 128 arterial segments to represent realistically the dimensions and branching patterns found in humans. Each segment is modelled as a thin, tethered viscoelastic tube. They investigated 'young' and 'old' models of the arterial tree, the difference between these models being the pulse wave velocity, which was 10.0 m s^{-1} for the 'old' model and 6.7 m s^{-1} for the 'young' model. The aortic input impedance of arterial tree simulations was presented for both models with different reflection coefficients at arterial terminations.

At low frequencies, reduction of the reflection coefficient makes the phase of the aortic input impedance less negative and reduces the modulus. Therefore, changes in the phase of the aortic input impedance can be used to estimate changes in the modulus of aortic input impedance that occur with changes in wave reflection. The following equation uses the phase of the aortic input impedance, pulse wave velocity and frequency to predict the magnitude of the aortic input impedance. We developed the equation to provide an approximation (within 5%) to both the 'young' and the 'old' data presented by Karamanoglu and colleagues (when the appropriate values for the pulse wave velocity are used):

$$|\,Z_{\text{AII}}\,|_1 = \left(\frac{v}{10.0}\right)^{k_1 - k_2 \cdot \phi(Z_{\text{AII}})} \cdot \{a \cdot (\phi(Z_{\text{AII}}))^2 + b \cdot \phi(Z_{\text{AII}}) + c\} \text{ dyne s cm}^{-3} \qquad [3]$$

where k_1=0.836, k_2=0.00724 and a, b and c are found from the following formulae:

$a=0.209\times(\ln(f))^2-0.461\times\ln(f)+0.696$

$b=2a\times(23.722\times\ln(f)+36.714)$

$c=2070.947+5.181\times(b-5.181a)$

For the PulseCO algorithm, pulse wave velocity in the thoracic aorta (v) is calculated from MAP as well as age and sex, using a relationship found by other workers.[6 19] A factor of 1.2 was included to relate the dynamic elasticity to the static elasticity.[20] Equation (3) provides a smooth interpolation of $|Z_{\text{AII}}|$ for different values of pulse wave velocity that are obtained.

Equation (3) requires the phase of the aortic input impedance. This is the difference between the phase of the aortic pressure and the phase of the aortic flow:

$$\phi(Z_{\text{AII}})=\phi(\text{aortic pressure})-\phi(\text{aortic flow}) \qquad [4]$$

$$\phi(Z_{\text{AII}})=\phi(\text{radial pressure})-\phi(T_{\text{A-RA}})-\phi(\text{aortic flow}) \qquad [5]$$

ϕ(radial pressure) can be calculated directly from the arterial pressure waveform. Approximations for $\phi(T_{\text{A-RA}})$ and ϕ(aortic flow) will be described.

Aortic flow

It is assumed that there is no flow in the proximal aorta during diastole, i.e. that there is a perfectly competent aortic valve. Approximations for (CO/|aortic flow|$_1$) and ϕ(aortic flow) are required from the radial artery pressure waveform (for equations (2) and (5)). The following equations are used:

$$\frac{\text{CO}}{|\text{ aortic flow }|_1} = A \times \left(0.5 + 0.45 \times \left(\frac{\text{ejection duration}}{\text{cycle duration}}\right)^2\right) \qquad [6]$$

$$\phi(\text{aortic flow})_1 = -145 \times \frac{\text{ejection duration}}{\text{cycle duration}} \qquad [7]$$

The aortic cross-sectional area (A) is calculated using the relationship derived by Langewouters and co-workers.[19] Only relative values of CO can be determined using pulse contour analysis because of the variability of aortic cross-sectional area between different subjects. In order to obtain absolute values, calibration with another device is required. The absolute CO is then obtained by multiplication with a calibration factor.

Equations (6) and (7) were derived from an ejection flow profile that was considered to be typical. As described in the Introduction, the heart interacts with reflected waves in different ways. An increase in wave reflection could result in the ejection waveform becoming more skewed to the left (especially if the ventricle was acting as a 'pressure source'). This would result in overestimation of $\phi(\text{aortic flow})_1$ and hence the increase in wave reflection would not be accounted for fully. However, the change in aortic input impedance would still be detected to some extent because the phase of the first harmonic of the arterial pressure is also influenced by the diastolic part of the waveform, in which the proximal aortic flow is stationary. These errors are also smaller when the ejection duration is short relative to the duration of the cardiac cycle.

Equations (6) and (7) might be improved by developing other indices of the pressure waveform to indicate situations where changes in the ejection profile have occurred. For example, detection of a biphasic ('bisferiens') pulse could indicate the unusual flow waveforms that can occur during hypertrophic cardiomyopathy.[14]

Aorta to radial artery pressure transfer ($T_{A\text{-}RA}$)

In addition to studies of aortic input impedance, Karamanoglu and colleagues used the same modelling techniques to investigate pressure transmission from the aorta to the radial artery.[18] The transfer function ($T_{\text{A-RA}}$) was obtained and plotted for a series of simulations in which several of the model parameters were varied. The results show that there may be considerable variation of the transfer function. However, the transfer function varies least in the low frequency ranges (those that are required for the first harmonic of the arterial pressure) and studies in humans have shown this variation to be less than expected.[28 29] The equations used to approximate $T_{\text{A-RA}}$ are:

$$|\,T_{\text{A-RA}}\,|_1 = 1 + \frac{f^2}{8.5} \qquad [8]$$

$$\phi(T_{\text{A-RA}})_1 = 20 \times f \qquad [9]$$

Equation (9) represents the phase difference relative to the phase shift that occurs because of the transit time. Equations (8) and (9) agree well with published experimental data obtained in humans.[28 29] It is assumed that these equations would also be appropriate for the relationship between aortic and brachial artery pressure.

The use of our algorithm with femoral artery pressure is not advisable. The most important sites of wave reflection with respect to aortic input impedance are the vascular beds of the trunk.[17] Changes in the reflection coefficient of these beds would be expected to change the relationship between the pressure in the ascending aorta and that in the abdominal aorta (as well as arteries distal to this). For this reason, the algorithm should be used with arterial pressure obtained from the upper limb. Pressure measured in the ascending aorta could also be used if equations (8) and (9) are omitted.

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Transoesophageal echocardiography in cardiac and vascular surgery: implications and observer variability

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Transoesophageal echocardiography (TOE) has gained widespread acceptance among cardiac anaesthetists as a tool to facilitate peri-operative decision-making. This observational study analyses the impact of TOE and its inter-observer variability on intra-operative patient management during cardiac and major vascular surgery. From June 1996 to December 1998, standardized reports were obtained from 11 anaesthetists in 1891 adult cardiac and vascular surgery patients undergoing routine biplane or multiplane TOE. Inter-observer variability and the difference between variables of interest were tested using the chi-squared test or factorial analysis of variance as appropriate. TOE examinations were performed before and after the operation; 1673 (88.5%) patients underwent cardiopulmonary bypass (CPB), and 218 (11.5%) patients had surgery without CPB, including 42 (2.2%) coronary revascularizations. In 923 patients (49%), TOE provided additional information that influenced the patient's therapy. In 968 patients (51%), TOE had only minor or no impact on clinical decision-making. In two patients (0.10%) the scheduled operation was not performed, and in another two patients the TOE examination led to major complications. Observer-dependent variables were: implications of TOE for intra-operative decision-making ($P<0.0001$), estimation of image quality ($P<0.0001$), pre-operative left ventricular fractional area change (FAC) ($P=0.0026$), difference between pre-operative FAC and post-operative FAC ($P=0.033$), and requests for supervision ($P<0.0001$). There was no significant difference in the case mix between observers. TOE had an important impact on intra-operative patient management. Inter-observer variability was significant for several variables but not for the frequency of additional surgical procedures.

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Indications for transoesophageal echocardiography (TOE) in the peri-operative period in cardiac and non-cardiac surgery were classified by the Society of Cardiovascular Anesthesiology and the American Society of Anesthesiologists in 1996.[1] Since then, several papers dealing with the implications of the routine use of TOE in cardiac surgery[2–7] and in major non-cardiac surgery[8–12] have been published. Other studies have addressed the problem of adequate imaging and inter-observer variability[13] and the need for quality control when using TOE.[14]

The aim of the present observational study was to analyse the impact of TOE and its inter-observer variability on peri-operative patient management during cardiac and major vascular surgery.

Methods

Intra-operative TOE is routinely performed at our institution by cardiac anaesthesia staff in the large majority of cases of cardiac surgery and major vascular (thoracic and abdominal aorta, carotid artery) surgery, except in patients with an overt contraindication and when a TOE probe is not available. Since June 1996, all anaesthetists performing peri-operative TOE have been asked to complete standardized report forms during the examination.

Anaesthesia and insertion of the TOE probe

Patients were pre-medicated with oral benzodiazepines (flunitrazepam or midazolam). In the operating theatre,

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anaesthesia was induced, the patient's trachea was intubated, and the lungs were mechanically ventilated. After insertion of a central venous catheter and a pulmonary artery catheter (if considered necessary), the latex-sheathed TOE probe was inserted, usually with an Esmarch manoeuvre or with the help of direct laryngoscopy if necessary.

TOE examination

Examinations were performed by a staff anaesthetist who was supervising a resident in charge of routine anaesthesia. Two Hewlett-Packard machines (HP Sonos 1500; Hewlett-Packard, Andover, MA, USA), initially with a biplane and later a multiplane 5-MHz TOE probe, and a Vingmed machine (CFM 800; Vingmed Sound, Horten, Norway) with an omniplane 5-MHz probe were used. A thorough TOE examination was performed, including injection of an air-saline emulsion via the central venous catheter into the right atrium after a ventilator-stimulated Valsalva manoeuvre (application of positive end-expiratory pressure (PEEP) of 20 cm H_2O, followed by release of PEEP and immediate injection of the emulsion) to detect or rule out a patent foramen ovale. Examinations were recorded on videotape according to the standard procedure. Less experienced observers had the opportunity to call for advice from a more experienced anaesthetist at any time. A cardiologist's help was available by means of a video line between the operating theatre and the TOE laboratory during daytime or by direct advice in the operating theatre.

Reporting, analysis of data and surgical consequences

To ensure adequate quality, a TOE-database/reporting system was introduced in June 1996, and all staff cardiac anaesthetists were advised to complete reports during adult TOE examinations in the operating theatre. The number of reported examinations was compared with the number of effectively performed TOEs and calculated as a percentage of reported cases, based on comparison with a written list of all examinations.

Data collected in these reports included technique and ease of probe insertion. 'Easy' insertion was achieved when the observer was able to introduce the probe without effort and/or unexpected problems. Insertion was 'difficult' when additional manoeuvres were necessary (unplanned direct laryngoscopy, several trials of introducing the probe) and 'impossible' when introduction was not feasible with laryngoscopy and, therefore, without probable harm to the patient.

Subjective estimation of image quality was 'good' if endocardial borders could be visualized in all four segments of the left ventricular (LV) short-axis view; 'moderate' if sufficient information for clinical decision-making was achieved but all endocardial borders were not visible; and 'insufficient' if the observer was not able to see important structures (e.g. the anterior and lateral walls of the left ventricle) because of bad image quality.

For evaluation of systolic LV function, global LV function was classified as 'normal' (fractional area change (FAC) $\geqslant$50%), 'moderately impaired' (FAC 40–50%), or 'impaired' (FAC <40%). Regional wall motion abnormalities (RWMA) were assessed by online estimation at mid-papillary-muscle level in short- and long-axis views, and in four-cavity view (horizontal and longitudinal views of the left ventricle), as proposed by the American Society of Echocardiography.[15] RWMA were reported if contractility decreased by two or more grades between two examinations (before and after cardiopulmonary bypass (CPB) or pre-operatively and intra- or post-operatively) according to Bergqvist and colleagues.[16] If a new RWMA was observed, an additional venous aorto-coronary bypass was performed if the operating surgeon considered it to be beneficial. When this was not feasible or not thought to be necessary, the insertion of an intra-aortic balloon pump (IABP) was considered.

FAC was assessed before surgical incision and after haemodynamic stabilization after CPB or after completion of the surgical procedure in operations without CPB.

Tests of the anatomy and function of cardiac valves, the test for patent foramen ovale, and evaluation of ascending, arch, and descending aortas were performed. Aortic plaques were classified according to Montgomery.[17] In case of plaques grade IV and V in the ascending aorta/aortic arch, surgeons modified their procedure by avoiding any trauma to the aorta whenever possible.

The need for supervision and/or for a cardiologist's advice and the subjectively single most important impact of the TOE examination on peri-operative patient management were also reported.

Categories for therapeutic consequences were: 'none' (if the entire TOE examination did not supply any additional information useful for patient management); 'surgery OK' (if the observer's assessment of cardiac function after surgery revealed no new RWMA after coronary artery revascularization procedures and normal function after valve repair or replacement); 'drugs/fluids' (if drug treatment and/or fluid therapy was changed or extended because of the TOE examination); 'change of surgical procedure' (if the planned surgical procedure had to be adapted according to a new finding in the TOE examination); 'new diagnosis' (if peri-operative TOE exhibited a previously unknown diagnosis, e.g. patent foramen ovale, subvalvular aortic stenosis, or new RWMA); or 'other.'

Evaluation of neurological outcome

Neurological outcome was assessed clinically by staff members of the intensive care unit before the transfer of the patient to the ward. If focal or generalized neurological damage was suspected or overt during routine examination, a consultant neurologist was asked to confirm the diagnosis.

Statistical analysis

Differences between observers and between variables of interest were analysed using the chi-squared test or with factorial analysis of variance as appropriate. P values of <0.05 were considered significant.

Results

Between June 1996 and December 1998, a total of 1891 TOE reports were completed by 11 cardiac anaesthetists. In the same period, 2296 examinations were performed, resulting in an overall reporting performance of 82.4% (74.4, 90.4) (mean, 95% confidence interval) (Table 1). The percentage of reported TOE examinations varied significantly between observers ($P<0.0001$).

The total number of cardiac and major vascular operations performed during this time was 2762, and the percentage of TOE examinations was 83% (81% for cardiac and thoracic aortic surgery, 85% for major vascular surgery).

Table 1 Transoesophageal echocardiography (TOE) examinations performed and reported by 11 observers. *Chi-squared=2390, $P<0.0001$

Observer	Previous experience (no. of TOEs)	Examinations performed	Examinations reported	Per cent reported
A	>300	211	195	92.4
B	>300	177	176	99.4
C	>300	194	89	45.9
D	>300	519	430	82.9
E	>300	345	288	83.5
F	150–300	228	177	77.6
G	150–300	181	140	77.3
H	150–300	105	86	81.9
I	<100	106	105	99.1
K	<100	166	146	88.0
L	<100	64	59	92.2
Total		2296	1891	82.4*

The 11 cardiac anaesthetists who performed the examinations had various levels of experience in peri-operative TOE (Table 1). Five anaesthetists had performed more than 300 TOEs before the survey began; during this study, they accomplished 1178 (62.3%) of the reported examinations. Three anaesthetists who had previously performed 150–300 TOEs carried out 403 (21.3%) of the reported examinations. The remaining three anaesthetists, who had performed fewer than 100 TOEs, performed 310 (16.4%) of the reported examinations (Table 1).

Probe insertion and complications

Ease and complications of probe insertion were reported from 1997 on, resulting in 1660 completed records: 1608 (97%) of the probe insertions were performed with a simple Esmarch manoeuvre, and 47 (2.8%) insertions were performed with direct laryngoscopy. Insertion was 'easy' in 1612 (97%) patients, 'difficult' in 26 (1.6%), and 'impossible' in five (0.3%). Complications of TOE were: arterial hypertension >30% of baseline value in 48 patients (2.4%), coughing in three patients (0.15%), tooth damage in two patients (0.1%), severe arrhythmia in one patient, hypopharyngeal perforation in one patient with Zenker diverticulum,[18] and a bleeding gastric mucosal lesion in one patient with previously unknown situs inversus abdominalis.

The complications required drug therapy in 27 (1.6%) patients, post-operative treatment by a dentist in two patients (0.1%), intra-operative gastroduodenoscopy and local treatment of a bleeding lesion in the patient with situs inversus, and immediate operation and prolonged treatment in the intensive care unit for the patient with the hypopharyngeal perforation.

Table 2 Types of operation and therapeutic implications. *Chi-squared=309; $P<0.0001$, dependent on type of operation with CPB; †chi-squared=28.5; $P=0.0015$, dependent on type of operation without CPB; ‡chi-squared=71.5; $P<0.0001$; operations with CPB versus operations without CPB. CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting

Operation performed	Total		None		Drugs/ fluids		Surgery OK		Change of surgical procedure		New Diagnosis		Other	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
With CPB														
CABG	916	48.4	386	42.1	182	19.9	170	18.6	92	10.0	64	7.0	21	2.3
CABG+vascular surgery	64	3.4	10	15.6	22	34.4	12	18.8	11	17.2	7	10.9	2	3.1
Other	170	9.0	38	22.4	45	26.5	41	24.1	16	9.4	26	15.3	3	1.8
Valve	523	27.7	51	9.8	72	13.8	277	53.0	55	10.5	31	5.9	37	7.1
Total CPB/% of all operations	1673	88.5	485	29.0	321	19.2	500	29.9	174	10.4	128	7.7	63	3.8*
Without CPB														
CABG	42	2.2	22	52.4	6	14.3	7	16.7	3	7.1	4	9.5	0	0.0
Other	53	2.8	25	47.2	7	13.2	8	15.1	2	3.8	4	7.5	6	11.3
Vascular surgery	123	6.5	63	51.2	39	31.7	4	3.3	3	2.4	11	8.9	3	2.4
Total non-CPB/% of all operations	218	11.5	110	50.5	52	23.9	19	8.7	8	3.7	19	8.7	9	4.1†
Total CPB and non-CPB/% of all operations	1891	100.0	595	31.5	373	20.4	519	28.7	182	9.6	147	5.2	72	3.8‡

Types of operation and main consequences of TOE

The types of operation for which TOE examinations were performed and the therapeutic consequences are presented in Table 2. The distribution of main consequences differed significantly between intervention with CPB and operations without CPB ($P<0.0001$). In isolated on-pump coronary artery bypass grafting (CABG) procedures, quality control ('surgery OK') was rarely reported; these examinations had the lowest percentage of consequences. The same was true for the off-pump CABG cases.

For the valve procedures and for the combined CABG procedures (CABG+vascular surgery), the incidence of therapeutic consequences was higher, and quality control ('surgery OK') was more important.

In the 123 vascular surgery procedures without CPB (mainly carotid endarterectomy and abdominal aortic surgery), more than 80% of all TOE examinations had only minor or no impact on patient management.

Tests for patent foramen ovale were performed in 1188 (63%) of all examinations. The diagnosis of a patent foramen ovale constituted 38% (54 cases) of the category 'new diagnosis' and was found in a total of 63 cases (5.3% of the 1188 examinations). In the remaining cases with a

Table 3 Type of additional intervention based on TOE examination. CABG, coronary artery bypass grafts; IABP, intra-aortic balloon pump; PFO, patent forearm ovale; CPB, cardiopulmonary bypass; LA, left atrial

Additional intervention	*n*	Per cent of all interventions	Per cent of all examinations
Second pump run	9	4.9	0.48
Additional CABG	17	9.3	0.90
Additional CABG and IABP	22	12.1	1.16
IABP	60	33.0	3.17
MV replacement, not repair	6	3.3	0.32
No operation	2	1.1	0.11
No valve replacement	4	2.2	0.21
PFO closure	6	3.3	0.32
Reperfusion CPB	5	2.7	0.26
Composite graft	2	1.1	0.11
Repair of ascending aortic dissection	1	0.5	0.05
LA marsupialization	2	1.1	0.11
CABG with CPB	1	0.5	0.05
Replacement IABP (was in vena cava)	1	0.5	0.05
Resternotomy	7	3.8	0.37
Other	11	6.0	0.58
Not reported	26	14.3	1.4
Total number/total %	182	100.00	9.6

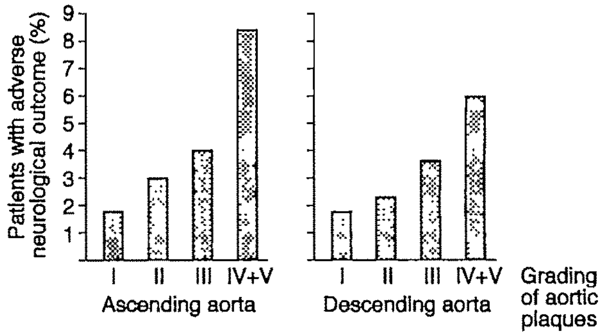

Fig 1 Ascending and descending aortic plaques and neurologic outcome. Grading of aortic plaques: I=minimal, II=extensive intimal thickening, III=plaques <5 mm, IV=plaques >5 mm, V=mobile plaques (according to Montgomery[17]).

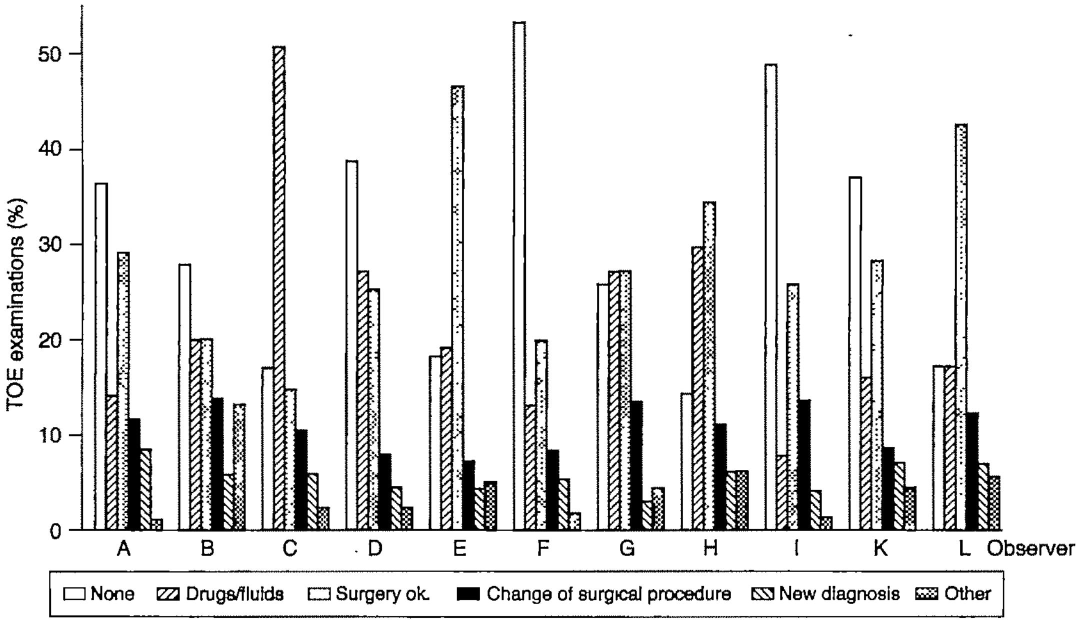

Fig 2 Subjective ratings of therapeutic implications of TOE by 11 observers; n=1891. The ratings were observer dependent; chi-squared=305; $P<0.0001$.

'new diagnosis', a new RWMA or a severe LV or right ventricular pump failure was present in 64 cases (43.5%). The remaining new diagnoses were a post-operative paravalvular leak after implantation of a prosthetic valve (three cases), a severe mitral insufficiency that was not corrected (three cases), an LV thrombus (two cases), and a variety of other diagnoses, such as LV outflow tract obstruction and severe aortic insufficiency in ascending aortic dissection (21 cases).

Additional interventions based on the TOE examinations are listed in Table 3. One-third of the 182 interventions consisted of intra-operative insertion of an IABP. Additional CABG was necessary in 39 (21.4%) cases. In two cases, the pre-operative TOE examination indicated that no operation was needed: an 80-yr-old woman undergoing mitral valve repair or replacement showed no mitral insufficiency in the TOE examination under anaesthesia, even after an increase in systemic

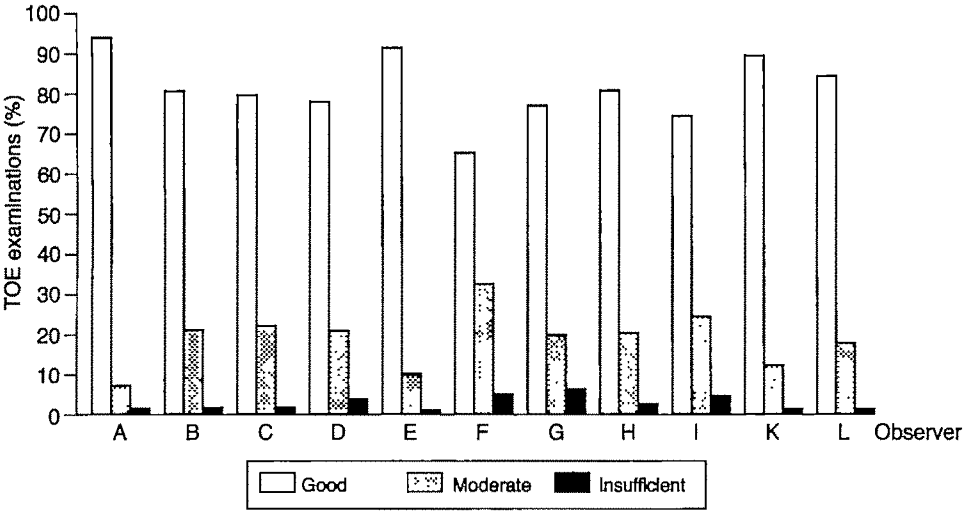

Fig 3 Subjective ratings of TOE image quality by 11 observers; n=1723 (168 missing values). Total ratings were 'good', 1394 (80.9%); 'moderate', 299 (17.4%); and 'insufficient', 30 (1.7%). The ratings were observer dependent; chi-squared=89; P<0.0001.

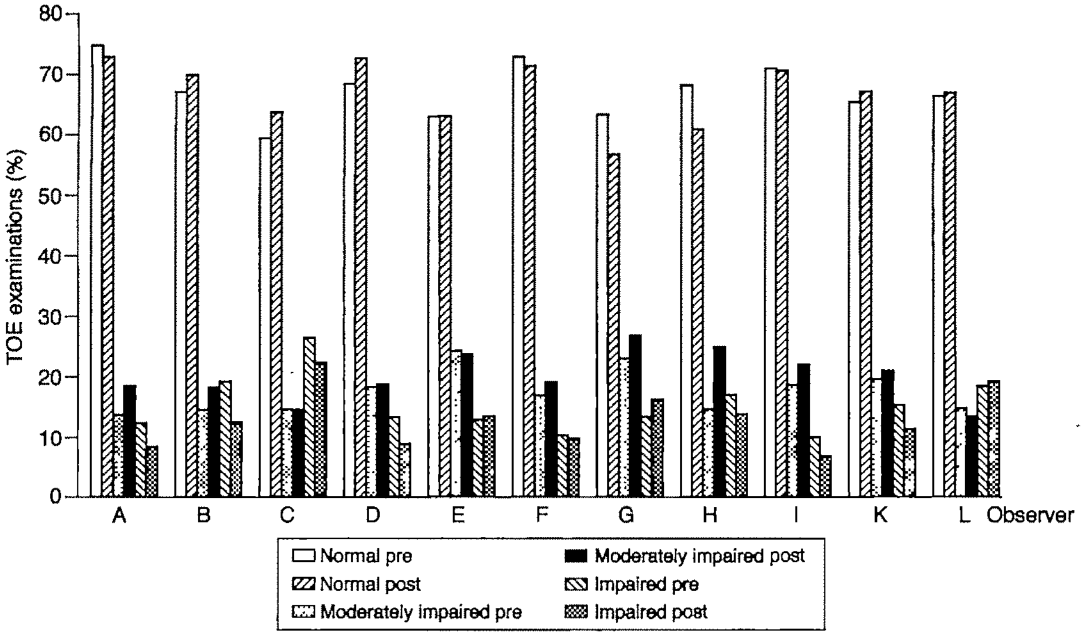

Fig 4 Estimation of fractional area change (FAC) by 11 observers. The first set of two bars represents FAC estimated pre- and post-operatively and rated as normal. The second set of two bars represents FAC estimated pre- and post-operatively and rated as moderately impaired. The third set of two bars represents FAC estimated pre- and post-operatively and rated as impaired. Pre-operative FAC and the difference between pre- and post-operative FAC (ΔFAC) were observer dependent. Pre-operative FAC: chi-squared=34; P=0.026; ΔFAC chi-squared=58; P=0.033. Total pre-operative ratings (n=1745 (146 missing values)) were 'normal', 1183 (67.8%); 'moderately impaired', 316 (18.1%); and 'impaired', 246 (14.1%). Total post-operative ratings (n=1764 (127 missing values)) were 'normal', 1203 (68.2%); 'moderately impaired', 358 (20.3%); and 'impaired', 203 (11.5%).

Table 4 Requests for supervision by an anaesthetist or a cardiologist. $^+$The column headed 'requests for either or both' does not simply represent the total number of requests. If both an anaesthesiologist and a cardiologist were called, the request was counted as only one. *Chi-squared=452, P<0.0001 between observers; †chi-squared=237, P<0.0001 between experience level; **chi-squared=427, P<0.0001 between observers; ‡chi-squared=218, P<0.0001 between experience level

	Previous Experience (no. of TOEs)	**Requests for anaesthetist**	**Requests for cardiologist**	**Requests for either or both$^+$**	
Observer		***n***	***n***	***n***	**% of all examinations performed**
A	>300	3	9	12	6.3
B	>300	2	17	19	19.8
C	>300	0	7	7	14
D	>300	4	29	33	9.7
E	>300	10	20	27	9.4
F	150–300	7	7	13	7.4
G	150–300	0	13	13	23.6
H	150–300	10	3	13	15.7
I	<100	63	5	65	62.5
K	<100	16	8	24	16.4
L	<100	12	5	15	25.4
		* †		** ‡	
Total number/total %		127	123	241	12.7

vascular resistance with norepinephrine administration. Therefore, after consultation with a cardiologist, she was considered for medical treatment instead. In a 68-yr-old woman undergoing removal of an intra-cardiac fibroelastoma, the tumour was not found in the pre-operative TOE examination, and she did not undergo an operation.

Aortic plaques and neurological outcome

The neurological outcome of 1357 cases was entered into our database beginning in January 1997. Forty-two patients (3.1%) suffered from focal or generalized neurological damage after surgery. Intra-operative extension of aortic plaques of the ascending and of the descending aorta (Fig. 1) was correlated significantly with adverse neurological outcome (P<0.05). For the ascending aorta, the number of patients in each grade (see legend to Fig. 1 for definitions) was: I, 13/765 (1.7%); II, 11/371 (2.9%); III, 2/49 (3.9%); IV+V, 1/11 (8.3%) (P=0.049). For the descending aorta, the number of patients in each grade was: I, 10/567 (1.7%); II, 8/353 (2.2%); III, 8/217 (3.6%); IV+V, 4/64 (5.9%) (P=0.031).

Cardiologist's advice

A cardiologist's advice was requested in 123 (6.5%) of the 1891 reported TOE examinations. The diagnosis was confirmed in 105 cases (85.3%); in 18 cases (14.6%) a new diagnosis was established. The new diagnosis led to a change in operative procedure in five cases (4%) and had no therapeutic consequences in 13 cases (10.6%).

Inter-observer variability

There was no significant difference between observers for the types of operation for which TOE was performed. Individual observer-dependent variables are shown in Table 1 and in Figures 2–4. For therapeutic consequences (Fig. 2), variability was very large for 'none', 'drugs/fluids', and 'surgery OK'. Variability for 'change of surgical procedure' and 'new diagnosis' was not statistically significant. The ratio of reported to performed examinations (Table 1), testing for patency of the foramen ovale (not shown), image quality (Fig. 3), and pre-operative LV FAC and the difference between pre- and post-operative FAC (Fig. 4) were all significantly observer dependent. Catecholamines were used in 11% of all patients (observer-dependent range from 0 to 26%). Catecholamine use was not associated with the difference between pre-operative and post-operative LV FAC.

Inter-observer variability in requests for supervision by an anaesthetist was highly significant and dependent on the experience level of the observer. Variability in requests for a cardiologist's advice was not significant (Table 4).

Discussion

The most important findings of this analysis of 1891 intra-operative TOE examinations are the following:

(a) Intra-operative TOE examinations contributed to patient management in cardiac surgery, even in isolated CABG procedures. (The 10% incidence of 'change of surgical procedure' following CABG represented 92 patients who profited from the examination.) For major vascular surgery, the consequences of TOE on intra-operative decision-making consisted mainly of modification of drug and fluid application.

(b) The percentage of reported examinations, most of the subjective ratings (e.g. interpretation of the consequences of TOE in patient management), and qualitative and semiquantitative measurements (e.g. FAC) were clearly observer dependent.

(c) The more objective consequences, however, such as a new diagnosis or a change of surgical procedure, varied much less between observers, and variability was not statistically significant.

(d) The search for quality improvement was evidently not futile, because younger colleagues needed significantly more supervision than did those with greater experience.

(e) The neurological outcome of the patient population was significantly worse when the size of aortic plaques increased, a fact that might suggest that TOE examinations in this specific field are reproducible.

Major limitations of this study

The ratio of reported to performed TOE examinations was effectively observer dependent, as was the quality of individual record keeping.[13] The 11 observers performed different numbers of TOE examinations and had different levels of experience. Thus, we would expect a significant observer-dependence because of individual differences in skill. On the other hand, there were also important differences in interpretation between equally experienced observers.

In such an observational study it is somewhat cumbersome to provide data for the effect of TOE on patient therapy. The impossibility of clearly defining criteria for record keeping for 11 anaesthetists can be illustrated by the detection of new post-operative RWMA. With such a finding, is the consequence a 'new diagnosis' (new RWMA) or the fact that additional drugs were applied? Therefore, we decided to leave to the observer's discretion the consequence that seemed to be the most important. When TOE led to such an important consequence as the change of surgical procedure, for example, additional CABG because of detection of a severe new RWMA, then the consequence of this particular TOE was clear.

Another cause of error may be over interpretation of the importance of the TOE examination. While 82 IABP insertions (4.3% of reported examinations) were reported to be a direct consequence of the TOE examination, a total of 140 IABPs (7.6%) were inserted during operations in which a TOE examination was performed. Therefore, almost half of the IABP insertions were not reported to be a direct consequence of the TOE examination.

An often-cited limitation of intra-operative TOE is the fact that it is impossible for the anaesthetist to perform anaesthesia and echocardiography at the same time.[19] Because of the status of our institution as a university teaching hospital, our staff members supervise the senior residents performing anaesthesia in almost all cases, so they are usually not restricted in this way.

We did not present outcome data beyond the immediate post-operative period (with the exception of neurological outcome), and it may be argued that this early post-operative outcome may not be decisive for final outcome after surgery. For complications of TOE, the same is true: we looked only at overt intra-operative complications. More subtle problems, such as late swallowing problems or sore throat,[20] were not taken into account. The aim of this study, however, was to evaluate the influence of TOE on intra-operative decision-making. The fact that the most important consequence (change of surgical procedure) was detected in as many as 184 patients (the two patients without operation included) makes the usefulness of intra-operative TOE evident.

The diagnosis of patent foramen ovale was made upon studying the atria during a microbubble injection only. Schneider and colleagues,[21] reported a small series of patients at autopsy and detected one missed diagnosis made with microbubbles alone; this corresponds to a sensitivity of 89%. Screening with colour Doppler echocardiography was not routine in our study, so our reported incidence of patent foramen ovale (5.3%) is low. It is also low when compared with other autopsy results, in which a 15–25% incidence of patent foramen ovale was found.[22 23]

The interpretation of information that is known to be difficult to obtain (e.g. high quality images of the ascending aorta[24 25]) will scatter as a function of the number of observations and the number of observers. Nevertheless, a correlation between aortic pathology and neurological outcome was found to be present.

According to our data, one may speculate that the usefulness of TOE in individual situations may also be observer dependent. The fact that TOE interpretation was more uniform for change of surgical procedure and new diagnoses, however, shows that a certain level of agreement was reached, sometimes with the help of either a supervising senior colleague or a cardiologist.

Comparison with results from other studies

Comparison of our results with those of other studies is not easy because of the non-uniformity of the impact classification and the fact that our anaesthetists had to define the single most important impact on intra-operative decision-making. It was, therefore, not possible for them to choose multiple factors, even if more than one important diagnosis resulted from the TOE examination.

A large series published by Mishra and colleagues[6] also came to the conclusion that peri-operative management is influenced by TOE in valve surgery and in CABG surgery. Interestingly, they found that TOE helped or modified surgical decisions in as many as 27% of the CABG patients and in 11.6% of the valve surgery patients. The surgeons in that study revised the coronary grafts in 0.8% of the cases, compared with 2.1% in our population.

Mishra and colleagues reported changes of surgical procedure in CABG patients as 'minor changes in planned surgery' without specifying what those minor changes were. They reported 4.9% 'major changes in planned surgery', which were also not specified, but this number is a lot closer to our finding of 10% surgical consequences in CABG patients. The high incidence of unsuspected findings in Mishra's study (11.6% of the valve procedures, 4.9% leading to major changes in planned surgery) is probably because of the fact that their patients were not given routine pre-operative transthoracic echocardiography (TTE) examinations. In our study, all valve surgery patients and a very large number of CABG patients had pre-operative TTE examinations by a cardiologist to rule out additional structural abnormalities that would have been overlooked by angiography.

The results from the study of Bergquist and colleagues[7] who evaluated 584 interventions in 75 CABG patients, are comparable with ours. The most important contributions of TOE were an indication for fluid administration (30%), anti-ischaemic therapy (21%), and critical surgical interventions (3%).

Whether modification of intra-operative fluid management should be considered a major or minor consequence for patient therapy may be debatable. However, the fact that fluid management, with the help of TOE, is very effective and rapid has been shown by Greim and colleagues.[26]

There were significant differences between cardiac surgery and major vascular surgery in the impact of TOE in our study. Non-cardiac surgery had a lower number of major consequences. Suriani and colleagues[11] reported an 81% incidence of TOE impact on intra-operative decision-making in non-cardiac surgery, but TOE was performed in a selected, high-risk patient population on demand of the attending anaesthetist. In our study, TOE was performed routinely in all major vascular surgery cases and still resulted in an overall TOE impact of 50%.

Series of different sizes involving complications of TOE[27–29] and several case reports of severe complications[18 30 31] have been reported. The incidence of severe pharyngeal lesions in awake patients seems to be well below 1% (Vignon,[29] 0.13%; Daniel,[27] 0.02%; Chan,[28] none). The data for complication rates of intra-operative TOE examinations in anaesthetized patients, however, are sparse. The incidence in our series was 0.1%. Fortunately, the two patients survived the complications. Since the study was completed, no serious complications have occurred at our institution, and our overall reported percentage of serious complications is approaching 0.05%.

This study was conducted with the help of standardized reports that all anaesthetists performing intra-operative TOE were supposed to complete. The percentage of reported examinations reached 82.4% and differed widely between observers. This is in accordance with results from a quality assurance programme reported by Rafferty[13] 6 yr ago. The overall reporting frequency in that study was 88%, and inter-observer variability was clearly demonstrated as well. Unlike Rafferty, we did not evaluate the quality and completeness of video recording, but frequent reviewing of tapes at our institution showed that we must improve imaging and storing on tape. Inter-observer variability of some variables has been reported: record keeping and image quality,[13] FAC,[15] intra-operative decision-making,[7] theoretical background, and image interpretation.[14] It is probably not possible, however, to eliminate observer variability by more intensive training, as it is very difficult to convince experienced anaesthetists to use uniform anaesthetic techniques and/or decision algorithms for any given clinical situation. It seems possible, however, that different observers come to reproducible and nearly identical conclusions regarding LV function.[32]

Evaluation of atheromatous plaques in the thoracic aorta is not without difficulties: Konstadt and colleagues[18] showed that TOE is sensitive in the ascending aorta in 100% of cases, is specific for atheromatous disease in 60%, and has a positive predictive value of only 34% but a negative predictive value of 100%. Hartman and colleagues[33] showed a high reproducibility among three observers but only 57% interpretable images of the ascending aorta. We have shown that, even though it is difficult to obtain sufficient image quality in the ascending aorta, adverse neurological outcome is higher, in accordance with the increasing severity of TOE-detected atheromatosis of the ascending and descending aortas.

In conclusion, despite great inter-observer variability in certain variables related to the TOE examination, observer dependence for operative consequences was not significantly different. TOE had a considerable impact on patient management in this study, including cases of isolated coronary artery revascularization. A probable benefit for 182 patients was the fact that the surgical procedure was changed, and for two patients the planned operation was not performed; the money saved in these two cases alone would pay for almost one-third the cost of a complete echocardiography machine.

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Intercurrent drug therapy and perioperative cardiovascular mortality in elective and urgent/emergency surgical patients[†]

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The Oxford Record Linkage Study (ORLS; an epidemiological database) was used to examine relationships between intercurrent cardiovascular drug therapy and cardiac death within 30 days of elective or emergency/urgent surgery under general anaesthesia. Cases identified from the ORLS were paired with matched control patients. Clinical details were obtained from the patients' medical notes. In elective surgical patients, there was no effect of β-adrenoceptor or calcium entry channel blockade, diuretics or digoxin on cardiac death after adjusting for confounding variables. Use of nitrates was associated with an odds ratio of 4.79 [95% confidence interval (CI) 1.01–22.72] for cardiac death after adjustment for confounding by a history of angina and residual age difference. In emergency/urgent patients, there were significant univariate associations with cardiac death for intercurrent use of angiotensin converting enzyme (ACE) inhibitors (odds ratio 1.18) and diuretics (odds ratio 4.95; 95% CI 1.82–13.46). However, neither maintained significance after adjustment for the confounding effect of cardiac failure. We conclude that, with the possible exception of the use of nitrates in elective surgical patients, chronic intercurrent drug treatment alone does not significantly affect the odds of cardiac death within 30 days of surgery.

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In high-risk patients undergoing major non-cardiac surgery, there is evidence that treatment with β-adrenoceptor blocking antagonists started before surgery and continued into the post-operative period can reduce cardiac mortality up to 2 yr after operation.[1 2] There are no published data on the effects of chronic β-adrenoceptor blockade on cardiac mortality and no data for any associations between other cardiovascularly active drugs (especially diuretics, digoxin, nitrates, calcium channel entry blocking drugs and angiotensin converting enzyme (ACE) inhibitors) and outcome from elective non-cardiac surgical procedures under general anaesthesia. Furthermore, there are no studies examining the interaction between drug therapy and cardiac death in urgent/emergency surgical patients.

We have reported previously on the use of a large epidemiological database [the Oxford Record Linkage Study (ORLS)] to examine the risk factors for cardiovascular death in the 30 days after elective and urgent/emergency surgery under general anaesthesia.[3–5] In these studies, we identified three risk factors associated with cardiac death in elective non-cardiac surgical patients (a previous myocardial infarction, a history of arterial hypertension, and renal failure), while in urgent or emergency surgical patients only the history or presence of congestive heart failure was a significant risk factor. Many of our patients were receiving intercurrent drug therapies for the management of underlying medical problems.

We have re-analysed our data to search for any associations between chronic β-adrenoceptor blockade or other intercurrent therapies and peri-operative cardiovascular death within 30 days of surgery in both elective and urgent/emergency surgical patients.

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Methods

The ORLS covers the former Oxford Regional Health Authority area and contains data on all hospital admissions and deaths in the area. We used the database to identify patients who died within 30 days of anaesthesia and surgery after elective or urgent/emergency admission to hospital, together with matched controls. The population chosen for this study comprised patients who were admitted to one of three hospital groups within the Oxford region and who died of a cardiac cause after either elective surgery (n=115) or urgent/emergency surgery (n=73) under general anaesthesia between 1979 and 1992. Because of the non-availability of some hospital records, the timescales of the two study populations overlapped but were not identical.

We included only patients aged over 18 yr who were undergoing non-cardiac or non-neurological operations (predominantly abdominal, vascular and orthopaedic surgery). For the area covered by the ORLS (relative to England as a whole), the standardized mortality ratios (SMRs) for diseases of the circulatory system were 85 for men and 89 for women in 1990; the corresponding SMRs for ischaemic heart disease were 83 and 81.

Cases

For each study, patients who had died within 30 days of anaesthesia and surgery and whose death certificate included ICD9 codes (9th International Classification of Diseases) in the range 401–438 inclusive at any position on the death certificate were identified. The diseases covered by these codes are hypertensive heart disease (401–405), ischaemic heart disease (410–414), diseases of the pulmonary circulation (415–417), other forms of heart disease (420–429) and cerebrovascular disease (430–439). We excluded patients dying from pulmonary embolism (415.1). There are also specific codes within ICD9 relating to complications associated with anaesthesia (e.g. 995.4 for shock as a result of anaesthesia, and 997.1 for cardiac arrest or insufficiency resulting from an operative procedure). As reported previously,[3–5] these codes were not used as a certified cause of death in any of the patients in the study population.

Controls

For each patient, at least one control was identified through the ORLS. Where possible, two or more controls were sought to allow for the possible non-availability of the medical case records. For the elective surgical patients, controls were matched according to the following criteria: (i) underwent the same operation as the patient; (ii) under the care of the same consultant as the patient; (iii) age within 5 yr of that of the patient; (iv) same sex as the case patient.

For the urgent/emergency surgery patients, the matching criteria for the controls were slightly different—age was within 10 yr of the case and there was no matching for sex. These criteria were relaxed to generate a larger number of control subjects, as it was felt that our earlier study of elective surgery suffered from over-matching.[4]

When two control patients were identified, one was chosen at random and the notes were obtained. If these were not available, or if this control was excluded for other reasons, the notes of the second control patient were examined.

Examination of the medical records

Before the study, we obtained consent to examine case and control patient records from the consultants caring for the patient during the surgical admission. Where a consultant had died or retired, the consent of his or her successor was sought. All notes were examined in detail by a research nurse (YMS). Whenever possible, the cause of death was confirmed from the notes to ascertain that the cause on the death certificate was supported by the medical records. If the patient had not died from a cardiovascular cause, he or she was excluded from the study. Physical characteristics of the patients and information on cardiovascular risk factors were collected using criteria described elsewhere.[4 5] In the case of drug therapies, these were noted where patients had received them for more than 1 month before hospital admission.

Data handling

A computer database was written using Microsoft Access (version 2.0) to store and examine the data. Microsoft Excel (version 6.0) was used to examine the tables produced by Access. Statistical analysis was performed using Stata (version 5.0) (STATA Corporation; College Station, TX, USA). Data were exchanged between the various programs using DBMScopy (version 5.10) (DBMScopy Software Inc.; Houston, TX, USA). All programs were run on a Viglen 233 MHz Pentium II desktop computer.

Statistical analysis

For matched data, univariate analysis was carried out and crude odds ratios were calculated as the ratio of the discordant pairs. Because subjects were matched for age over a wide interval (±5 yr in the elective surgical patients, and ±10 yr in the urgent/emergency surgical patients), there was potential for residual confounding by age within pairs. Adjustment was therefore made for within-pair age difference, using conditional logistic regression. This provides a useful statistical correction for within-pair age difference but does not give a direct description of the effect of age on peri-operative risk. In the urgent/emergency surgery patients, adjustment was similarly made for within-pair sex differences.

Multivariate analyses were performed to examine the associations between cardiac death and the various

Table 1 Results for the association of individual drug therapies and cardiac death in elective surgical patients. Data are crude and age-adjusted odds ratios together with the 95% confidence intervals (CI). *P* values refer to the age-adjusted odds ratio, and were calculated using the Wald test. *Lower CI estimate; no point estimate calculable. n.s.=not significant

	Odds ratio (95% CI)	**Age-adjusted odds ratio (95% CI)**	***P***
β-Adrenoceptor blockade	1.64 (0.81–3.45)	2.04 (1.00–1.17)	0.05
Calcium channel entry blockade	4.67 (1.30–25.32)	4.35 (1.20–15.79)	0.026
ACE inhibitors*	(0.19)	(0.19)	n.s.
Diuretics	2.36 (1.23–4.77)	2.51 (1.28–4.92)	0.008
Digoxin	3.50 (1.10–14.60)	4.13 (1.24–13.79)	0.021
Nitrates	5.50 (1.87–21.96)	6.04 (1.97–18.29)	0.002

Table 2 Conditional logistic regression model for the effects of β-adrenoceptor blockade and calcium entry channel blockade on cardiac death within 30 days of elective surgery, adjusted for hypertension, angina and residual confounding by age. Data are odds ratios together with the 95% confidence intervals (CI). *P* values were calculated using the Wald test

	Odds ratio (95% CI)	***z* score (Wald test)**	***P***
β-Adrenoceptor blockade	1.00 (0.41–2.44)	0.007	1.0
Calcium entry channel blockade	1.61 (0.36–7.12)	0.62	0.53
Hypertension	2.04 (1.0–4.13)	1.97	0.049
Angina	2.57 (0.91–7.27)	1.8	0.074
Age difference	0.82 (0.73–0.93)	3.2	0.001

cardiovascular medications after adjusting for confounding. For each drug examined, statistical adjustment was made for the indications for prescription of that therapy. For example, in the case of β-adrenoceptor blockers and calcium channel entry blocking drugs, adjustment was made for the effects of arterial hypertension and angina, and in the case of diuretics adjustment was made for the effects of congestive cardiac failure and hypertension.

Alternative regression models were compared using the log likelihood ratio test. The significance of individual terms in the final models was examined with the Wald test.[6] This test was performed by dividing the coefficient ratio obtained from the regression model by its standard error to obtain a standard normal deviate. The *P* value was obtained using a table of probabilities. By this method, we examined the effects of chronic treatment with β-adrenoceptor blockers, calcium channel entry blockers, diuretics, nitrates and digoxin. The small numbers of patients receiving ACE inhibitors prevented the drug being examined in a regression model.

The results generated by the analyses are shown as odds ratios and their 95% confidence intervals (CI).

Results

Elective surgical patients

Among the elective surgical patients, we identified 177 patients who died of a cardiovascular cause with 30 days of surgery under general anaesthesia; 115 of these were studied further after matching with controls. Of the other 62 patients, 37 were excluded because either the notes of the patient, control or both were missing, and the other 25 because no matched control could be identified.

The mean age of the cases was 73 yr (range 45–93) and that of the controls 71 yr (43–90). In 74 (64%) of the pairs, the case and the control were male. Twenty-four cases and 15 controls were taking β-adrenoceptor-blocking drugs, 16 cases and five controls were taking calcium channel entry blocking drugs, two cases and no controls were taking ACE inhibitors; 48 cases and 29 controls were taking diuretics, 24 cases and six controls were taking nitrates, and 15 cases and five controls were taking digoxin. A significantly greater number of the cases were receiving calcium channel entry blockers, diuretics, digoxin and nitrates. The causes of death in the cases were myocardial infarction/ischaemic heart disease (78 deaths), heart failure (23) and cerebrovascular accident (14).

The crude odds ratios for the association of individual drug therapies and adverse outcome and the adjusted ratios for confounding by residual age difference between the case-control pairs are shown in Table 1. Univariate age-adjusted ratios showed significant associations with cardiac death for calcium channel entry blockade, diuretics, digoxin and nitrates ($P<0.05$), and a significance of $P=0.05$ for β-adrenoceptor blocking drugs. The effects of β-adrenoceptor blockade and calcium channel blockade were examined together in a conditional logistic regression model, which also contained terms for arterial hypertension and angina, and a term to allow for the effects of residual confounding by age. Full details of the model are given in Table 2. In this model, the odds ratio for the association between the use of β-adrenoceptor blockade and postoperative cardiac death was 1.00 (95% CI 0.41–2.44); $z=0.007$, $P=1.0$. The odds ratio for the association of calcium channel entry blockers and cardiac death was 1.61 (0.36–7.12); $z=0.62$, $P=0.53$. The addition of a term for interaction between β-adrenoceptor blocking drugs and calcium channel antagonists did not improve the model significantly. That is to say, there was no evidence in elective surgical patients of interaction between β-adrenoceptor antagonists and calcium entry blocking drugs.

Table 3 Results for the association of individual drug therapies and cardiac death in urgent/emergency patients. Data are crude and age- and sex-adjusted odds ratios together with the 95% confidence intervals (CI). *P* values refer to the age- and sex-adjusted odds ratio, and were calculated using the Wald test. *Lower CI estimate; no point estimate calculable

	Odds ratio (95% CI)	**Age- and sex-adjusted odds ratio (95% CI)**	***P***
β-Adrenoceptor blockade	5.00 (0.56–236.45)	5.11 (0.59–44.20)	0.138
Calcium channel entry blockade	3.50 (0.67–34.53)	3.57 (0.73–17.48)	0.117
ACE inhibitors*	(1.18)	(1.18)	0.032
Diuretics	4.60 (1.71–15.49)	4.95 (1.82–13.46)	0.002
Digoxin	2.50 (0.92–7.86)	2.61 (0.99–6.90)	0.053
Nitrates	1.75 (0.45–8.25)	1.93 (0.54–6.82)	0.310

For the other drug therapies, there were no significant associations between diuretics or digoxin and cardiac death after the confounding effects of arterial hypertension, heart failure and other drug therapies (i.e. β-adrenoceptor blocking drugs and calcium channel entry blocking drugs) had been taken into account. There was, however, a significant association between administration of nitrates and cardiac death after adjustment for the confounding effects of pre-existing angina and residual age difference [odds ratio 4.79 (95% CI 1.00–22.72); z=1.943, P=0.049]. After adjustment for the effect of any associated administration of β-adrenoceptor blockade, the odds ratio increased to 5.72 (1.09–25.54); z=2.065, P=0.039.

Urgent and emergency patients

In the urgent/emergency patients, we identified 202 cases; controls were found for 73 of them. Of the 129 patients excluded, 34 underwent surgery under local or regional anaesthesia, 24 were admitted as emergency patients but initially received medical treatment rather than surgical care (surgery taking place some days after admission), 25 had untraceable notes or no matched control and 45 did not fulfil the study criteria (18 having pulmonary emboli, three non-cardiovascular causes of death and 24 being incorrectly coded); the remaining patient died on the way to the operating theatre. Death was due to myocardial infarction/ischaemic heart disease in 34 patients, cardiac failure in 16, cerebrovascular accident in 14, and other cardiac causes in the remaining nine.

The mean age of the cases was 81 yr (range 40–98) and that of the controls was 81 yr (43–100). Five cases were receiving β-adrenoceptor blocking drugs and seven were receiving calcium channel entry blockers; the corresponding controls included one patient on β-adrenoceptor blockers and two on calcium channel entry blockers. For the other drug treatments, six cases and no controls were receiving ACE inhibitors, seven cases and four controls were receiving nitrates, 39 cases and 21 control were receiving diuretics, and 16 cases and seven controls were receiving digoxin. In the urgent/emergency patients, more cases were receiving diuretics and ACE inhibitors.

There were no significant univariate associations between β-adrenoceptor blocking drugs, calcium channel entry blocking drugs or nitrates and cardiac death in the urgent/emergency surgical patients; however, after adjusting for sex and residual age difference between the case–control pairs, there were significant associations between diuretics and ACE inhibitors and cardiac death (Table 3). As with the elective surgical patients, there was no interaction between β-adrenoceptor blockade and calcium channel entry blocking drugs

After adjusting for the effects of other confounders (such as angina, arterial hypertension and heart failure) by logistic regression analysis, there were no associations between drug therapies and cardiac death. In the case of diuretic therapy, the addition of a history of heart failure to the regression model reduced the odds ratio for diuretics from 4.29 to 1.94, while a history of heart failure reduced the odds ratio for digoxin from 2.61 to 1.34 (both final odds being non-significant).

Discussion

In this case–control study, we found no significant association in elective or emergency surgical patients between chronic β-adrenoceptor blockade and cardiac death within 30 days of anaesthesia. The analyses presented here were prompted by the conflicting findings of several other groups of researchers.[1 2 7 8]

In a randomized controlled trial of atenolol versus placebo, Mangano and colleagues demonstrated a reduction in mortality 6, 12 and 24 months after hospital discharge in patients randomized to receive the β-adrenoceptor blocking drug before operation and for 7 days after surgery.[1] The main effect of atenolol treatment was seen in the first 6 months after surgery, but no difference in in-hospital mortality was observed.

In a second study, Poldermans and colleagues reported on 112 high cardiac risk patients with evidence of dobutamine stress-inducible echocardiographic (ECHO) abnormalities scheduled for major vascular surgery.[2] After randomization, the treatment group received oral bisoprolol for at least 1 week before surgery, and continued until 30 days after operation. The incidence of cardiac deaths in the bisoprolol group during the 30-day peri-operative period was only 3.4% compared with 17% in the control group. There was also a difference in the incidence of non-fatal myocardial infarction (0% in the bisoprolol group *vs* 17% in the control group). In a subgroup consisting of 53 patients already maintained on β-adrenoceptor blocking drugs, there were four post-operative cardiac deaths (7.5%) and no non-fatal infarctions. These results are in contrast to the data of Mangano and colleagues, who found no effect of acute atenolol compared with placebo on in-hospital deaths.[1]

In two further studies in patients undergoing vascular surgery under general or regional anaesthesia, Yeager and colleagues found β-adrenoceptor blockade was associated with a 50% reduction in peri-operative myocardial infarction, but they do not report on peri-operative mortality,[7] while Oliver and colleagues also found no effect of β-adrenoceptor blockade on the incidence of either myocardial infarction or cardiac death in patients receiving mivazerol or placebo.[8]

There are differences in study design between our study and these other studies. The latter used randomization of patients from high-risk populations for cardiovascular disease to ensure a comparable distribution of risk factors between the treatment and placebo groups. On the other hand, our observational study depended on examining the possible effects of chronic β-adrenoceptor therapy, having made statistical adjustments for the influence of other cardiovascular risk factors. Specifically, adjustment was made for the indication for the prescription of the various medications. In the analysis of the data for elective surgery, we included terms for the two main indications for the prescription of β-adrenoceptor blocking drugs: arterial hypertension and angina. These differences may help explain the contrast between our findings and those of Mangano and colleagues[1] and Poldermans and colleagues.[2]

More recently, studies have shown that use of β-adrenoceptor blockade in patients with mild to moderate heart failure may have a significant effect on cardiac outcome in these high-risk patients.[9] Two studies have found β-adrenoceptor blockade to be associated with a reduction in total cardiac mortality and all-cause hospitalizations in patients with heart failure.[10] [11] The interaction of anaesthesia, β-blockade and heart failure has not yet been evaluated fully. In our present study populations, there were few patients who had a history of heart failure and were receiving β-adrenoceptor blocking drugs (four among the elective surgical patients and two in the urgent/emergency patients). However, there were no differences in death rates between patients who had a history of heart failure and who were receiving β-adrenoceptor blocking drugs compared with patients not receiving this treatment.

Another possible explanation for the difference between acute and chronic β-blockade is that patients on long-term cardioselective β_1 antagonists do not maintain sustained blockade as a result of β_1 receptor adaptation. This could result from either receptor up-regulation or a compensatory increase in cardiac β_2 receptors, or a combination of the two.[12] An alternative explanation might be that of inverse agonism by chronic β-blockade at G-protein-coupled receptors, as has been demonstrated *in vitro* in rat fibroblasts by Milligan and colleagues.[13]

There have been a number of studies examining the effects of medication with calcium channel antagonists on cardiac death in patients with stable angina or after infarction.[14–16] There are few comparable data on cardiac outcomes in non-cardiac surgical patients receiving intercurrent calcium channel entry blocking drugs. We found an increased incidence of post-operative silent myocardial ischaemia in patients receiving calcium channel entry blocking drugs.[17]. Mangano and colleagues demonstrated an association between pre-operative calcium entry blocking drugs and post-operative ischaemia in non-cardiac surgical patients.[18] However, multivariate regression analysis failed to support this association, or an association with either in-hospital or long-term mortality in US Veterans Administration male patients undergoing non-cardiac surgery.[19]

There have been reports that short-acting calcium channel entry blocking drugs (such as nifedipine) may be associated with an increased risk of cardiovascular events, including cardiac death. Thus, Psaty and colleagues found an association between short-acting calcium channel entry blocking drugs and the increased risk of myocardial infarction in hypertensive patients.[20] However, this was not borne out in two further studies in patients receiving calcium channel entry blocking drugs for chronic coronary artery disease[21] or hypertension.[22]

It is unlikely that the regression models used in our analyses make a complete adjustment for confounding risk factors for the effects of either chronic β-adrenoceptor or channel entry channel blockade. However, the fact that the odds ratios for both treatments moved towards unity after adjustment suggests no independent effect of these drugs.

The slight association between nitrate administration and adverse cardiac outcomes in the elective surgical patients was surprising. However, Ishikawa and colleagues have shown long-term nitrate therapy given to post-infarction patients to be associated with an increased incidence of cardiac events, including cardiac death.[23] There are no data on post-surgical cardiac complications in patients on long-term nitrates, although five studies have looked at their effects on perioperative ischaemia. Two studies show a significant reduction in intraoperative ischaemia[24] [25] while three others show no effect.[26–28] The differences in outcome may reflect differences in underlying anaesthetic technique (volatile *vs* opioid-based) or differences in study populations. Our data may indicate the need for high-risk cardiac patients receiving only nitrates to be given additional anti-ischaemic drugs in the perioperative period.

Other researchers have noted increased perioperative mortality associated with emergency surgery.[29–31] In our cases who underwent urgent or emergency surgery, there were no significant associations between β-adrenoceptor or calcium channel entry blockade and 30-day cardiac death. Although diuretics and ACE inhibitor therapy had significant associations with cardiac death on univariate analysis, these effects were rendered non-significant by adjustment of the data for confounding factors (especially heart failure). The implication is that the risk associated with these drugs was due to the conditions for which they were prescribed. Heart failure is universally accepted as a strong predictor of post-operative myocardial infarction, reinfarction and worsening left ventricular function,[32] and cardiac death.[33]

In conclusion, our case–control study failed to show any significant effect of chronic β-adrenoceptor blockade on 30-day survival after either elective or urgent/emergency non-cardiac surgery. However, the CIs for the death rates after urgent/emergency surgery were wide, and we suggest that further studies using large databases, such as the ORLS, are warranted. Although chronic calcium channel entry blockade was associated with adverse cardiac outcome in elective surgical patients by univariate analysis, this was not sustained after adjustment for the effects of hypertension and angina. In the emergency or urgent surgery patients, there was a significant association between digoxin therapy and cardiac death, supporting the findings of Hollenberg and Mangano, who showed that pre-operative digoxin therapy was a significant predictor of post-operative silent myocardial ischaemia and hence cardiac events.[34] However, after adjustment for confounding due to a history of cardiac failure (a well-established risk factor for cardiac death following anaesthesia and surgery),[5 33] digoxin therapy did not remain a significant risk factor. As with our previous publications, caution should be exercised because of the assumed low power of the study, as indicated by the small numbers of patients receiving the therapies and the resulting large CIs of the odds ratios.

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The auditory evoked response as an awareness monitor during anaesthesia

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We investigated the relationship between the latency of the Nb wave of the auditory evoked response (AER) and periods of awareness during propofol anaesthesia. In the anaesthetic room before cardiac surgery the AER was recorded continuously in 14 patients. Awareness was measured by the ability of the patient to respond to command using the isolated forearm technique (IFT). The Nb latencies were shorter when the patients were able to respond than at loss of response ($P<0.001$). In six patients who repeated this transition from response to loss of response, there was a high and significant correlation between Nb latencies. None of the patients had any recollection of events after the initial induction of anaesthesia as measured by explicit and implicit memory tests. These results suggest that the Nb latency of the AER may represent an indication of awareness in individual patients, but wide inter-patient variability limits its practical usefulness. In addition, because no evidence of memory was demonstrated, even when patients were known to be awake, the relationship between AER and memory processing remains unclear.

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Keywords: brain, auditory evoked response; anaesthetics i.v., propofol; measurement techniques, isolated forearm technique; anaesthesia, depth; memory, implicit

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Changes in the middle latency auditory evoked response (AER) reflect changes in anaesthetic depth,[1–3] and to some extent changes as a result of surgical stimulation (Fig. 1).[4 5] Some studies have attempted to use the AER to distinguish between consciousness and unconsciousness during target-controlled infusions of propofol.[6 7] The AER technique, however, has rarely been correlated with objective evidence of awareness such as the isolated forearm technique (IFT),[8] or with implicit memory.[9 10]

We examined the correlation between the latency of wave Nb of the AER and periods of awareness, determined by the ability to respond to command with an isolated forearm. The response to verbal command can be distinguished from the response to surgical stimulation, as it must involve some degree of cognitive processing, rather than a simple reflex type movement. To establish the extent of this cognitive processing we also presented lists of words before the induction of anaesthesia and during periods of awareness for use in post-operative tests of implicit memory. Previous evidence has suggested that autonomic reflexes are not reliable measures of anaesthetic depth,[11] but these are still used in everyday anaesthetic practice. We therefore also observed the relationship between episodes of awareness and arterial pressure.

Patients and methods

After approval for the study from the Southampton Joint Research Ethics Committee and written informed consent, we studied 14 patients (aged 54–75 yr, ASA II or III) having cardiac surgery. Patients were introduced to the study by means of an information sheet explaining the use of the AER and IFT, and they were informed that a number of word lists would be played during the anaesthetic room procedure. Patients with poor left ventricular function, more than moderate valvular stenosis, hearing difficulties or any past medical history of epilepsy or mental illness were excluded from the study, as were those with a high pre-operative anxiety score as measured by the Hospital Anxiety and Depression Scale.[12]

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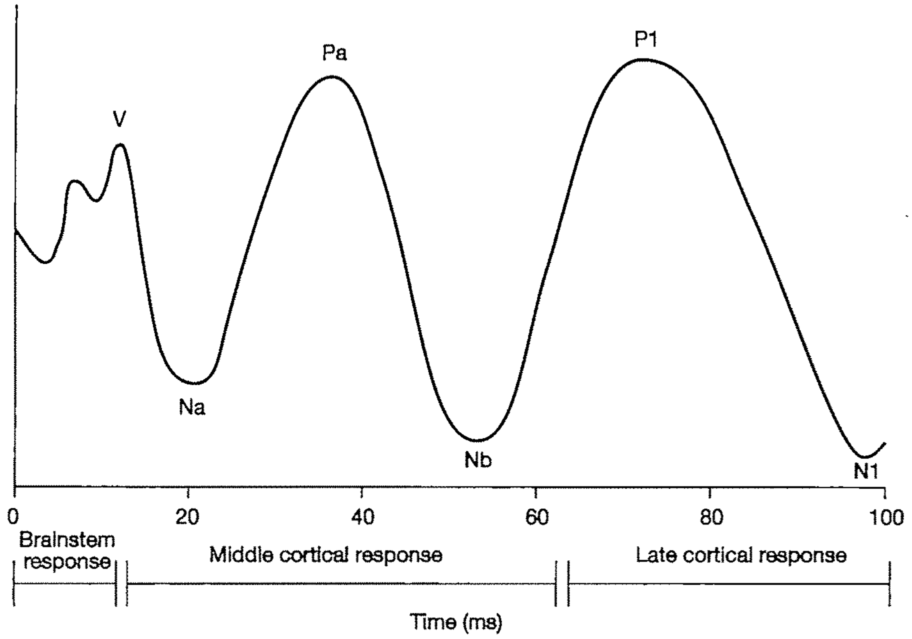

Fig 1 Schematic representation of the AER.

Pilot studies in spontaneously breathing patients showed that it was impossible to record a meaningful AER when the patients were awake or lightly sedated because of interference from muscle artefact. We therefore used response to command with the IFT as our indicator of awareness. To eliminate the confounding effect of surgical stimulation, the entire procedure was undertaken in the anaesthetic room before surgery. After pre-medication with oral diazepam 10 mg, i.m. morphine 10 mg and prochlorperazine 12.5 mg patients were taken to the anaesthetic room approximately 1 h before the scheduled time for surgery.

In the anaesthetic room full invasive monitoring with continuous recording, including automated ST segment analysis, was started according to standard practice in our unit. The patient's free left upper arm was wrapped with soft surgical padding (Soffban; Smith and Nephew) and a padded orthopaedic tourniquet was placed over this. The AER was monitored using the Northwick Park system, as described previously.[13] Briefly, the EEG was recorded with a prototype amplifier, digital signal processor system (Loughborough Sound Instruments, Loughborough, UK) and bespoke software running on a 386SX personal computer. Disposable silver/silver chloride electrodes (MSB) were placed on Fpz and the two mastoids as in the International 10:20 system.[14] Closely fitting binaural ear pieces were used for delivery of both words and the auditory stimuli (clicks) for evoking the AER. The AER was generated by averaging 512 EEG epochs of 125 ms duration beginning at the click stimuli.

Sixteen words with comparable occurrence frequencies were divided into four lists. The words were selected from a previous implicit memory study in non-anaesthetized volunteers, in which they were found to have similar priming rates (Loveman, van Hooff and Gale, submitted for publication). Each list of four words was recorded onto a compact disc and copied five times. For the post-operative implicit memory tests the same female voice was used for the recording. A compact-disc player presented the first list of words (five times) before induction of anaesthesia with fentanyl 100 μg and propofol 1 mg kg^{-1}, followed by an infusion of propofol at 2 mg kg^{-1} h^{-1}. As soon as consciousness was lost (absence of eyelash reflex) the tourniquet was inflated to 300 mm Hg and vecuronium 0.1 mg kg^{-1} was administered. After tracheal intubation, mechanical ventilation of the lungs was commenced and adjusted to an end-tidal carbon dioxide tension of 4.5–5.0 kPa. When the AER was considered stable, the propofol infusion was turned off. At 1 min intervals the patient was called by their name and asked to squeeze the experimenter's hand. The request for response to command was made individually to each patient by the same experimenter. If patients had not responded after 20 min the tourniquet was deflated for 10 min and then re-inflated for a further 20-min period. Thus, the maximum inflation time for any patient was 40 min and all patients responded within this period.

When the first unequivocal response was made, the patient was reassured and informed that they were now going to hear another word list. This word list was again played five times. To enable clear hearing, the commands to squeeze the experimenter's arm were stopped during presentation of the word list. After presentation of the word lists, the propofol infusion was started again at a rate of 6 mg kg^{-1} h^{-1} for 10 min, reducing to 4 mg kg^{-1} h^{-1} for a further 10 min and then 3 mg kg^{-1} h^{-1} until the response to command was lost. All patients remained responsive to command after presentation of the word list. Testing for response continued each minute and when the response to command had been lost for 3 consecutive min the patient was then played the third word list (five times). All patients were unresponsive to command after the presentation of the third word list. A fourth and final word list was not presented to serve as a baseline measure and the order of the four word lists was rotated between patients. In six patients there was sufficient time to stop the propofol infusion again and repeat the above procedure without the word lists. The patients were then prepared for surgery.

Within 36 h of surgery, after having been transferred to the main ward, patients were assessed for both explicit and implicit memory. To establish any explicit recall of intra-anaesthetic events patients were asked the following four questions:[15]

What is the last thing that you remember before you were put to sleep for your operation?

What is the first thing that you remember on waking from your operation?

Do you remember hearing anything during the operation?

Did you dream of anything during the operation?

To assess implicit memory (defined as memory without conscious recollection[16]) patients were presented with 18 pre-recorded spoken word stems, corresponding to the first syllables of the 16 stimulus words of the four lists (e.g. PIC from PICNIC or MEL from MELLOW), plus two practice stems. They were asked to verbally complete each stem with the first word that sprang to mind (e.g. PIC can become PICNIC but also the more typical words such as PICTURE or PICKLE). The word stem completion test has been used successfully in previous anaesthetic studies[17] and is a commonly used method for assessing implicit memory in psychological investigations (for a review see Schacter[16]). Furthermore, the current word stem completion test, including the specific stimuli, the auditory presentation mode and the verbal response format, was previously validated in a study using healthy volunteers (Loveman, van Hooff and Gale, submitted for publication). In addition to this, a forced choice recognition task was undertaken. Patients were played a list of 28 words (the 16 words from the four lists plus 12 fillers) and asked to respond if they felt they remembered hearing any, or if any seemed familiar. This technique has also been used in anaesthetic studies.[17 18] Finally, explicit memory was reassessed with the question, do you remember squeezing the experimenter's hand at any time during the anaesthetic period?

Measurement of the latency of the Nb wave was undertaken off line by each author independently. Repeatability between us was significant, (r=0.93, P<0.05) and analysis was therefore continued with the scoring of one rater.

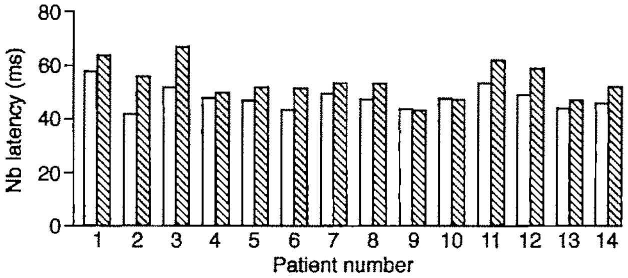

Fig 2 Individual changes in Nb wave latency with and without response to command of the isolated forearm.

Results

IFT

Despite the potential problems,[11] we found the IFT easy to apply, and had no difficulty using it or interpreting responses. The average time of first response to command was 15 min, with a range of 5–30 min. No patients were responsive at the first time of asking. In all patients an unequivocal response was given, with all patients being able to squeeze the experimenter's hand. No reported problems with the isolated arm were documented post-operatively. Patients stopped responding to command after commencement of the propofol infusion at between 4 and 10 min (mean time 6 min).

AER

The mean latency of Nb was 48.4 (SD 4.3) ms at first response to command and 54.6 (6.7) ms at loss of response to command. A paired samples t-test revealed that this difference in Nb latency was statistically significant (t=–5.11, df 13, P<0.001). The individual Nb latencies for each of the patients are shown in Figure 2. In all but two patients (patients 9 and 10) the Nb latencies were longer at loss of response than at response. However, the range of Nb latencies were quite large which illustrates the problem of specifying a general cut-off point. For example, a cut-off point of 60 ms, as suggested by Schwender and colleagues,[19] would in our study lead to a sensitivity of 100% (percentage of patients for which the presence of a response to command could be correctly predicted) but also to a very low specificity of 29% (percentage of patients for which the absence of a response to command could be correctly predicted). Similarly, a cut-off point of 51 ms[20] would result in a sensitivity of 79% and a specificity of 71%, and a cut-off point of 44.5 ms[8] would results in a sensitivity of 21% and a specificity of 93%.

In six patients we had time to make a second measurement of Nb latency with and without response to command (Table 1). Nb latencies for the first response (i.e. first measurement) were not different from those for the second response (i.e. second measurement) (t=0.425, df 5, P=0.68).

Table 1 Individual ranges of Nb latency in six patients with response to command and at loss of response

Patient no.	First movement	Second movement	First loss of movement	Second loss of movement
2	42	40	56	67
3	52	50	67	70
5	47	46	52	52
7	50	53	54	55
8	47	44	54	55
14	47	50	53	55
Mean	47.5	47.2	56.0	59.0

Table 2 Arterial pressure measurements (mm Hg) for 14 patients obtained at commencement of the study (baseline), on the first movement and when the movement had ceased

Arterial pressure	Minimum	Maximum	Mean	SD
Baseline	128.0	179.0	152.6	22.9
Movement	115.0	220.0	164.1	30.5
No movement	88.0	212.0	124.9	32.6

Furthermore, there was a high correlation between Nb latencies for first and second response (r=0.80, P<0.05). Similarly, Nb latencies for the first loss of response were not different from those for the second loss of response (t=−1.81, df 5, P=0.13), and the values correlated highly with each other (r=0.85, P<0.05).

Arterial pressure measurements

Arterial pressure measurements are shown in Table 2. A repeated measures ANOVA showed a significant main effect of recording period (F(2,22)=9.66, P<0.001). Planned comparisons showed significant differences between baseline and the first response to command of the isolated arm (t=−2.19, df=11, P<0.05), baseline and when responses were no longer present (t=2.43, df=11, P<0.05) and between the first response and first loss of response (t=4.06, df=11, P<0.01).

Explicit and implicit memory measures

Results of the five questions designed to establish evidence of explicit memory suggested that patients had no recollection of events during the study period, despite the fact that each patient made several responses to command during the study. In eight patients, the last thing remembered before induction of anaesthesia was before arriving in the anaesthetic room. The remaining patients had some recollection of i.v. cannulation procedures and only two patients could remember that a word list was played before induction of anaesthesia. These two patients were nevertheless unable to correctly recall the individual words. All patients, however, were responsive and co-operative when they arrived in the anaesthetic room. There was no evidence of implicit memory for any of the presentation conditions, including those for which it was known that patients were awake (i.e. before induction of anaesthesia and when responsive to command).

Discussion

A significant difference was demonstrated between the mean latency of Nb when movement occurred in response to command on the isolated forearm and when it ceased. In an early study Thornton and colleagues[8] compared the latency of the Nb wave with responses on the IFT in seven patients. Using light anaesthesia with N_2O, they suggested a threshold of 44.5 ms as a cut-off for awareness as demonstrated by the IFT. In two other studies, using averaged group data, an Nb threshold of 60 ms was predictive of cessation of spontaneous movement during both propofol and isoflurane anaesthesia without neuromuscular block[19] and in the region of 50 ms with no response to command or post-operative recall during isoflurane anaesthesia.[20] In our study the range of Nb latencies at which the transition occurred from the anaesthetized state to first response and from first response to no response of the isolated forearm was quite large. Some patients had no responses at latencies where others remained responsive. This finding hinders the definition of a general cut-off point in the latency of the Nb wave as a method of measuring awareness during anaesthesia.[2] With regard to our results, in order to reduce the possibility that any patients were deemed to be asleep but were actually awake, a cut-off point of 58 ms would be required (sensitivity 100%). However, this would mean that 71% of patients (specificity of 29%) would have to be anaesthetized to a point much deeper than just at loss of response.

High correlations were found between Nb latencies for the first and second measurements in all six patients who repeated the transition from response to no-response. This means that there is minimal hysteresis in the AER, with Nb latency at both periods of response to command and at both periods of loss of response to command being largely similar. This finding, although based on a small number of patients, adds further weight to the possibility of providing individual rather than general cut-off points for awareness during anaesthesia. However, the practical implications need to be the focus of further investigation.

Measurements of arterial pressure at response to command were significantly different from baseline (pre-anaesthesia), and at loss of response to command. It should be noted, however, that arterial pressure was not monitored throughout the experimental procedure, and that changes were measured at two single points in time, for example, response and no response of the isolated forearm. Thus, we cannot comment on what the arterial pressure was at other times.

Measures of memory

We found no evidence of implicit or explicit memory during anaesthesia. In the word stem completion task, manifestations of implicit memory would be a tendency to complete the word stems with the words recently encountered (i.e. before and during anaesthesia), but this was not found. Similarly, in the forced choice recognition task, implicit memory would be if patients recognized at least some of the presented words based upon feelings of familiarity, but this was not found. These results suggest that there is no memory, explicit or implicit, during anaesthesia. However, this does not account for the lack of priming effects for the word list presented in the pre-medicated state before anaesthesia induction, or for the word list presented during the anaesthesia period while patients were responsive to command, using the IFT. This finding is comparable to Russell's investigations with the IFT.[21]

Some studies using the word stem completion test[17] have demonstrated memory effects during general anaesthesia, and others have provided no evidence for implicit memory.[22 23] Similarly, a number of studies using sub-anaesthetic doses of anaesthesia in volunteers have found an inconsistent relationship between responsiveness during sedation and later recall, as measured by implicit or explicit measures of memory.[24] One difficulty with all these studies is that the depth of anaesthesia has not been assessed at the time of presentation. This means that it cannot be ruled out whether the memory effects demonstrated were because of period of inadequate or light anaesthesia.

Perhaps the implicit memory test may not be a reliable enough measure over such a period of time. Roediger and colleagues,[25] however, reported that implicit memory, as demonstrated by a word stem completion test, could persist for up to 1 week in normal populations. The lack of implicit memory in our study may reflect an effect on memory from prolonged anaesthesia and sedation (as patients are all sedated up to and during their stay on the intensive care unit).

In summary, we found a correlation between changes in wave Nb of the AER with changes in awareness as measured by the IFT. With the exception of two patients, individual latencies changed in the same direction with increasing depth of anaesthesia, although the variation between individuals was wide. This means that some patients were responding where others had stopped responding and as such reduces the application of the AER for anaesthetic monitoring. No evidence of memory for inter-anaesthetic events was demonstrated.

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Ocular microtremor: a tool for measuring depth of anaesthesia?

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Ocular microtremor (OMT) is a fine high frequency tremor of the eyes caused by extra-ocular muscle activity stimulated by impulses emanating in the brain stem. Several studies have shown that the frequency of this tremor is reduced in patients whose consciousness is reduced by anaesthesia or head injury. Therefore, OMT may possibly be used to determine depth of anaesthesia. Twenty-two unpre-medicated subjects undergoing surgery with general anaesthesia were studied. OMT activity was measured at admission using the open eye piezoelectric strain gauge technique. Anaesthesia was induced with propofol using a target controlled infusion delivery system (Diprifusor™). OMT activity was then recorded at predicted plasma propofol concentrations of 1, 2, 3 and 5 $\mu g\ ml^{-1}$. The patient's level of consciousness (response to command or stimulation) was assessed after each OMT measurement. OMT activity was reduced progressively at predicted plasma concentrations of propofol of 1 and 2 $\mu g\ ml^{-1}$ and then plateaued between 3 and 5 $\mu g\ ml^{-1}$. There was a significant difference between the last awake OMT recording and the first recording at loss of consciousness ($P<0.001$). OMT recording holds promise as a practical indicator of the depth of anaesthesia.

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At present the anaesthetist's main source of information on the depth of anaesthesia is the patients somatic and autonomic response to surgical stimuli. These responses are modified by neuromuscular block drugs and drugs affecting the autonomic nervous system. The presence or absence of these responses does not, however, correlate with conscious awareness[1] and they are inadequate indicators of a satisfactory depth of anaesthesia; therefore, the search for an adequate measure of the depth of anaesthesia continues.

Ocular microtremor (OMT) is a small high frequency tremor of the eyes present in all individuals. This tremor is caused by high frequency extra-ocular muscle stimulation which originates in the oculomotor area of the brainstem.[2] The oculomotor neurons are 'embedded in the reticular formation' of the brainstem.[3] However, neural activity from other areas outside of the brainstem impinge on the oculomotor nuclei. These include the frontal eye fields (areas 6 and 8),[4] the inferior parietal cortex (area 7)[5] and the cerebellum.[6] The OMT signal appears as an irregular oscillatory movement with intermittent burst-like components. The peak-to-peak rotation involves a displacement of the surface of the eye of between about 150 and 2000 nm.[7] The mean OMT peak count frequency in the normal population is 84 Hz (SD 6).[8]

The initial interest in OMT was stimulated by its purported role in the visual process, as part of the dynamic theories of vision.[9] More recently, the appreciation of OMT as a primarily neurological phenomenon has stimulated interest in its clinical applications.[1] Several studies have already shown that the frequency of this tremor is reduced in patients whose level of consciousness has been affected by head injury or anaesthesia.[1 10–12] Both Coakley[13] and Bolger[12] studied the effect of thiopental on OMT activity. Both studies showed a reduction in the high frequency components of OMT activity with a shift of the spectrum to the left, although the number of subjects studied was small. However, in the case of Coakley,[13] a number of agents were used including neuromuscular block.

It would therefore seem possible that OMT recordings could be used to determine depth of anaesthesia. The present study was undertaken to show the effect of general anaesthesia induced with propofol on OMT. Assessment

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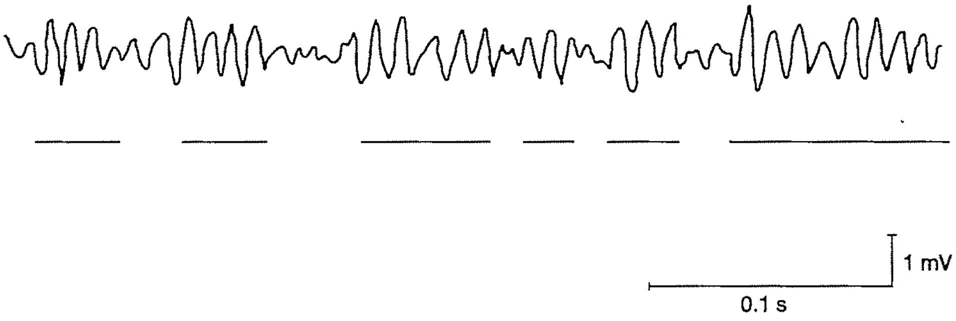

Fig 1 Example of a normal OMT recording in an alert individual. 'Bursts' are underlined and the period between the bursts is termed the baseline.

of the changes in OMT in the awake and unconscious state was also studied independent of the dose of propofol.

Methods

Subjects

After gaining local Ethics Committee approval and informed consent, 22 neurologically normal subjects undergoing general anaesthesia for general surgical procedures were studied. There were nine females and 13 males. The age range of the subjects was 38–71 yr. Subjects taking CNS depressant medication were excluded from the study. No pre-medication or opioid analgesia was given.

Recording session

OMT recordings were taken pre-operatively on the ward at admission using the piezoelectric strain gauge technique (baseline recording).[14] This technique has been described in detail elsewhere[7] and provides a reliable estimate of OMT activity.[15] Briefly, the piezoelectric transducer is mounted in a Perspex rod and the protruding end is coated with rubber. The subject lies supine looking straight ahead wearing a headset. During anaesthesia this eye position may change but studies by Bolger[12] have shown there is no significant overall variation in OMT mean peak count frequency with eye deviation. The subject's eyelids are taped apart and the scleral surface is anaesthetized with 0.5% hydroxymethacaine hydrochloride. The piezoelectric probe is mounted in the headset and lowered so the rubber tip is just touching the scleral surface. Probe placement is judged by visual inspection and by listening to the signal being recorded using audiocassette headphones. The signal is processed in a conditioning unit and then recorded on an audiocassette recorder. A recording of between 30 and 60 s was taken.[15] Analysis is performed on an IBM compatible PC with a special OMT processing package. An example of a normal OMT recording from an alert individual is shown in Figure 1.

Anaesthetic technique

The patients were monitored in the anaesthetic room with non-invasive arterial pressure, ECG and peripheral oxygen saturation. The only drug administered during the duration of the study was propofol, which was infused using a target controlled infusion system (Diprifusor™). All patients received supplemental oxygen via nasal cannulae at 4 litre min^{-1}. The Diprifusor™ TCI system consists of a microprocessor driven infusion pump (Graseby 3500), controlling the infusion rate of propofol based on a three compartmental pharmacokinetic model, a specific set of pharmacokinetic parameters[16] and algorithms for infusion control. The initial bolus required to reach the predicted blood concentration is given at 1200 ml min^{-1}. Thereafter the infusion rate is controlled to maintain the selected target concentration in the blood allowing for redistribution and elimination.

However, the model assumes immediate mixing in blood and takes no account of the delay required to achieve equilibration in the brain. Thus, a delay occurs between the time when a Diprifusor™ system indicates a target concentration has been reached and the time of maximum pharmacodynamic effect. Using a computer simulated model based on the Marsh pharmacokinetic parameters, it was clear that a period of 5 min would be long enough to allow steady state conditions to occur between the blood and effector site compartments.

The TCI infusion was started at a concentration of 1 μg ml^{-1} predicted blood propofol concentration and after a period of 5 min, allowing for equilibration, OMT activity was recorded and then the patient's level of consciousness was assessed. They were deemed to have lost consciousness if there was loss of response to verbal command and no eyelash reflex present.

The reading taken before this point, at the lower predicted blood propofol concentration, was termed the 'last awake' recording. The process was then repeated at predicted blood propofol concentrations of 2, 3 and 5 μg ml^{-1}. When all the required recordings had been made either the patient's trachea was intubated or a laryngeal mask inserted and anaesthesia maintained appropriate for the intended surgery.

Analysis of records

Each subject had a baseline OMT record and then between two and four further recordings at each different predicted plasma propofol concentration. OMT recording was diffi-

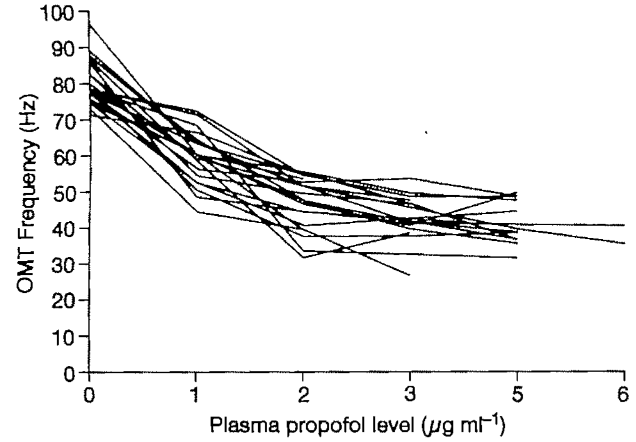

Fig 2 OMT (Hz) mean peak count frequency at different predicted plasma propofol concentrations.

cult in some subjects at different levels of awareness because of coughing or sneezing. Records were analysed using peak count analysis of dominant frequency. Comparison of peak count variables was performed using the Wilcoxon matched-pairs signed-ranks test.

Results

The mean peak count frequency of subjects before administration of propofol was 80.55 (SD 5.89) Hz and this fell to a mean frequency of 43.81 (7.33) Hz at loss of consciousness ($P<0.001$). The mean peak count was reduced to a value of 60.05 (7.12) Hz when the plasma propofol concentration was 1 μg ml^{-1} ($P<0.001$) and further reduced to a value of 47.77 (7.52) Hz at concentrations of 2 μg ml^{-1} ($P<0.001$). This reduction plateaued between concentrations of 3 and 5 μg ml^{-1} as shown in Figure 2. There was a significant difference between the mean peak count frequency of the last awake reading (mean 53.67 (7.47) Hz) and the first OMT recording at loss of consciousness (mean 43.81 (7.33) Hz), $P<0.001$. This is illustrated in Table 1. Ten subjects lost consciousness at a predicted plasma propofol concentration of 2 μg ml^{-1}. The other 11 subjects lost consciousness at concentrations of 3 μg ml^{-1}; in one subject readings were abandoned at 2 μg ml^{-1} because of coughing. However, there was no significant difference between the peak count frequency at loss of consciousness and the readings taken thereafter ($P<0.83$ for 2 μg ml^{-1} and $P<0.12$ for 3 μg ml^{-1} respectively) (Fig. 3).

Discussion

Plomley was the first, in 1847, to define depth of anaesthesia.[17] He described three stages: intoxication, excitement and deeper levels of narcosis. Since then, many descriptions of the depth of anaesthesia have been published including Guedel's[18] classic description of the clinical signs of ether anaesthesia. A variety of clinical monitors has been tested in order to assess depth of anaesthesia, including autonomic signs, EEG, isolated forearm technique, auditory evoked responses, oesophageal contractility and surface EMG, but each has its limitations.[19]

Table 1 Ocular microtremor (OMT Hz) mean peak count frequency at last awake and at loss of consciousness

Subject	Age	Last awake OMT (Hz) reading	First OMT (Hz) reading at loss of consciousness
1	52	61	54
2	53	52	48
3	45	59	32
4	63	73	55
5	51	40	27
6	65	55	50
7	57	45	40
8	44	53	45
9	71	53	41
10	71	49	45
11	56	47	41
12	49	51	38
13	70	53	54
14	47	69	34
15	45	52	46
16	68	48	40
17	36	52	42
18	53	56	50
19	63	48	42
20	64	55	49
21	62	56	47
Mean	57	53.67	43.81
SD	10	7.47	7.33
P		0.001	

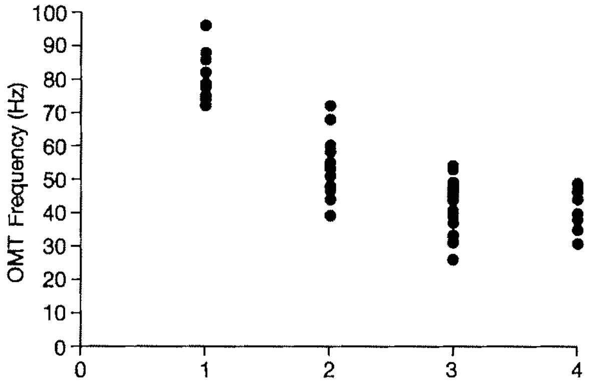

Fig 3 OMT (Hz) mean peak count frequency of the subjects studied at baseline (1), at the last awake (2), at first loss of consciousness (3) and when deeply anaesthetized (4).

Anaesthetic agents appear to have a predilection for the reticular activating system even if they do also act more diffusely in the brain. Recent studies by Rampil and colleagues[20] in rats support the hypothesis that anaesthetics have a primary action within the midbrain or lower. OMT is a high frequency tremor caused by impulses emanating from the oculomotor area in the brain stem. The oculomotor neurons are embedded in the reticular activating system.[3] Therefore, we would expect that agents affecting this area would also influence OMT activity.

This study confirms that ocular microtremor activity is affected by propofol. Previous studies by Coakley[13] and Bolger[12] also showed that OMT activity is affected by thiopental. In the study by Coakley[13] a number of agents were used, including neuromuscular block, and in all but two cases recordings were made with a closed eye transducer. The report by Bolger[12] studied only five patients. However, neither study gave details of induction times or assessment of levels of awareness.

This study has shown that the mean OMT peak count frequency is reduced progressively at predicted plasma propofol concentrations of 1 and 2 μg ml^{-1} and then plateaued between 3 and 5 μg ml^{-1}. Significantly, in this study no subject was conscious at predicted plasma concentrations of 3 μg ml^{-1} and at these concentrations none of the subjects had a peak count frequency above 55 Hz. After loss of consciousness, OMT activity remained below this level (55 Hz). There was no significant difference between mean peak count frequency at loss of consciousness and readings taken thereafter, even at increasing predicted plasma propofol concentrations. There is a significant difference between the last awake OMT recording and the first recording taken at loss of consciousness (P<0.001). The actual frequency at which subjects lost consciousness, however, was very variable—ranging from 27 to 55 Hz. It may be that a better predictor of the actual mean peak count frequency at which there was loss of consciousness in each subject would be to calculate a percentage of the baseline frequency for each subject. In this study, if we set a value of 45% of the baseline frequency for each subject, then 17 out of the 21 subjects had lost consciousness at this predicted OMT frequency (81%).

These results are encouraging and indicate that in the subjects studied OMT activity varies with awareness. With regards to depth of anaesthesia, we could postulate that any increase in OMT above the mean peak count frequency noted at loss of consciousness could indicate lightening of anaesthetic depth. It is interesting that studies of the effect of propofol on the auditory evoked response have shown no significant effect on the amplitude and latency of the brain stem waves.[21] In our study there is a clear effect on OMT, which has been shown to be an indicator of brain stem function.[1] However, if this is to be used in the clinical setting, more information is required on the effect of other agents on OMT activity such as opiates, neuromuscular block agents and, in particular, surgical stimulus. For continuous monitoring during anaesthesia, recordings will need to be made through the closed eyelid. These points are currently being investigated.

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Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia

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The bispectral index (BIS) and a sedation score were used to determine and compare the effect of propofol in the presence of fentanyl, alfentanil, remifentanil and sufentanil. Seventy-five non-premedicated patients were assigned randomly into five groups (15 in each) to receive fentanyl, alfentanil, remifentanil, sufentanil or placebo. Opioids were administered using a target-controlled infusion device, to obtain the following predicted effect-site concentrations: fentanyl, 1.5 ng ml^{-1}; alfentanil, 100 ng ml^{-1}; remifentanil, 6 ng ml^{-1}; and sufentanil, 0.2 ng ml^{-1}. After this, a target-controlled infusion of propofol (Diprifusor) was started to increase concentration gradually, to achieve predicted effect-site concentrations of 1, 2, and 4 μg ml^{-1}. At baseline and at each successive target effect-site concentration of propofol, the BIS, sedation score and haemodynamic variables were recorded. At the moment of loss of consciousness (LOC), the BIS and the effect-site concentration of propofol were noted. The relationship between propofol effect-site concentration and BIS was preserved with or without opioids. In the presence of an opioid, LOC occurred at a lower effect-site concentration of propofol and at a higher BIS_{50} (i.e. the BIS value associated with 50% probability of LOC), compared with placebo. Although clinically the hypnotic effect of propofol is enhanced by analgesic concentrations of μ-agonist opioids, the BIS does not show this increased hypnotic effect.

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Total intravenous anaesthesia, based on the administration of propofol combined with an opioid, has become a popular anaesthetic technique. It allows independent modulation of the different components of anaesthesia.[1] It is generally agreed that the anaesthetic effect of propofol is enhanced by the additional administration of an opioid.[2 3]

The bispectral index (BIS) has been proposed as a measure of the effects of anaesthetics on the brain.[4 5] Several authors have demonstrated that a good relationship exists between the BIS and blood concentration of propofol,[6–8] but, during propofol anaesthesia, increasing doses of alfentanil or additional administration of nitrous oxide do not affect the BIS value.[9 10] Several authors, using different anaesthetic techniques, examined the usefulness of the BIS as a measure of the 'depth of anaesthesia'.[11–13] Its reliability for the measurement of the hypnotic effect of propofol in association with different opioids has not yet been established definitively. We hypothesised that the effect-site concentration of propofol required for loss of consciousness (LOC) depends also on the simultaneous administration of opioids. The aim of this study was to measure the influence that analgesic concentrations of opioids had on the predicted effect-site concentration of propofol with relation to LOC and BIS values during induction of anaesthesia.

Patients and methods

The ethics committee of our institution granted approval for the study. Written informed consent was obtained from 75 ASA I or II patients scheduled for elective surgery. Patients were not premedicated. Using a random table, patients were divided into five groups (15 in each), one for each of the four opioids used and one for placebo. Patients who were taking psychotropic drugs (benzodiazepines, barbiturates or anti-epileptics) and obese patients (body mass index >30) were not included. Non-invasive arterial pressure, electrocardiogram, peripheral oxygen saturation and end-tidal carbon

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dioxide (AS/3; Datex, Engstrom, Finland) were continuously measured throughout the study period. An Aspect A-1000 (version 1.1, BIS 3.12; Aspect Medical Systems, Natick, MA, USA) was used to monitor the BIS. Four cutaneous electrodes (ZipPrep; Aspect) were positioned: At_1 and At_2 (one each above outer malar bones) with Fp (4 cm above nasion) as the reference and Fp_2 (left forehead) as the ground. Impedance was kept at <5000 ohms. The BIS (100=awake, 0=burst suppression) and its trend were displayed continuously.

After insertion of a peripheral venous line for fluid and drug administration (with an anti-reflux system (Abbott; Donegal, Ireland)) the following measurements were taken: arterial pressure, heart rate, Sp_{O_2}, BIS and sedation score (Observer Assessment of Alertness/Sedation Scale (OAA/S) (Table 1). The opioids or placebo were administered in a double-blind fashion to obtain preselected effect-site concentrations of 1.5 ng ml^{-1} for fentanyl (Janssen-Cilag AG, Baar, Switzerland), 100 ng ml^{-1} for alfentanil (Janssen-Cilag), 6 ng ml^{-1} for remifentanil (Glaxo-Wellcome AG, Bern, Switzerland) and 0.2 ng ml^{-1} for sufentanil (Janssen-Cilag). The anaesthetist who performed all clinical observations was blinded. A second, independent, anaesthetist was in charge of the opioid infusion according to the randomization. The opioid infusion was administered using a Graseby 3400/UK infusion pump and a Dell laptop computer using Stanpump software (Stanford University, Anesthesiology Service, Palo Alto, CA, USA) to control the effect compartment. The kinetic model was not weight-adjusted for fentanyl and alfentanil,[14] but was weight-adjusted for sufentanil[15] and remifentanil.[16] The target effect-site concentrations of opioids were maintained stable for 10 min before administration of propofol. Target-controlled infusion of propofol was started to increase predicted plasma concentration stepwise to 1, 2 and 4 µg ml^{-1} using a Diprifusor/Graseby 3500 UK pump with the kinetic set of Marsh for propofol. This device continuously displays the predicted effect-site concentration. At each step, the target plasma concentration was maintained for ⩾12 min to permit equilibration with the effect site. This 'steady state' was maintained for 2 min for each concentration. The BIS (three independent measurements), sedation score and haemodynamic variables were recorded during each steady-state period.

Simultaneously 100% oxygen was given via a facemask. When the sedation score decreased to 3, the evaluation was repeated every 30 s until LOC. Patients who responded to any verbal command (OAA/S between 5 and 3) were considered to be conscious. Those who did not respond to any verbal command and responded only after mild prodding or shaking were considered to be unconscious. Patient respiration, if necessary, could be assisted manually to maintain normocarbia. At the time when clinically LOC was deemed to have occurred, the BIS values and effect-site concentrations of propofol were recorded. Thereafter, rocuronium 0.6 mg kg^{-1} was administered for muscle relaxation and ventilation was manually assured. The study was concluded when the target effect-site concentration of propofol had been 4 µg ml^{-1} for 2 min. At this point it was disclosed if an opioid or a placebo had been administered. If a placebo had been used, sufentanil 0.2 µg kg^{-1} was given and the trachea intubated.

Table 1 Responsiveness scores of the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S)

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (alert)
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Statistical analysis

Statistical analysis was performed using GraphPad Prism v.2.01, Peakfit v.2.0 (Jandel Scientific Software) and SPSS v.6.1 for Windows 95. General logistic regression models (with limits of maximum and minimum fixed at 0 and 100, respectively) were used to analyse the correlation for the LOC. We determined the BIS value and the effect-site concentration of propofol at which 50% of patients lost consciousness (BIS_{50} and EC_{50}, respectively) for each group. The curve fit graph of the logistic regression displayed the 95% confidence interval for the fit, which was used to estimate the standard error of the predicted estimates for BIS_{50} and EC_{50}. Prediction probability (P_k) was calculated using Smith's definition.[17]

Differences in patient characteristics were analysed using *t*-test (for age, weight and height) or χ^2 test (for male–female distribution). The correlation coefficient for the relationship between sedation score and BIS was calculated for each group using a linear regression model. BIS values and haemodynamic variables were analysed within the groups, using analysis of variance (ANOVA) for repeated measurements.

Results

Data from 70 patients were analysed. Five patients were excluded from the study for technical reasons (poor signal quality from the EEG electrodes). Patients' characteristics were similar in all groups (Table 2). The mean (SD) duration of the study was 55 (5) min.

The correlation coefficient of BIS values and effect-site concentrations of propofol was similar in all groups (propofol–placebo, 0.98; propofol–fentanyl, 0.97; propofol–sufentanil, 0.96; propofol–remifentanil, 0.92; and propofol–alfentanil, 0.92).

The relationship between sedation score and effect-site concentration of propofol is illustrated in Figure 1. Patients

Table 2 Patients' characteristics. Values are mean (SD). There were no significant differences between groups

	Placebo (n=15)	Fentanyl (n=13)	Sufentanil (n=14)	Remifentanil (n=14)	Alfentanil (n=14)
Weight, kg	76.5 (16.5)	74.7 (13)	74.1 (12)	69.2 (11.3)	71.6 (8.3)
Height, cm	171 (10)	172 (9)	174 (9)	167 (7)	171 (9)
Age, yr	48 (28–65)	43 (28–72)	38 (26–66)	40 (20–69)	41 (24–59)
Gender, F/M	5/10	2/11	6/8	6/8	6/8

Table 3 Mean (95% confidence interval) bispectral index (BIS_{50}) and effect-site concentration in the different study groups. *Significant difference between propofol–opioid and propofol–placebo (P<0.001). †Significant difference between propofol–remifentanil plus propofol-alfentanil and propofol–fentanyl plus propofol–sufentanil (P<0.01). ‡Significant difference between propofol–opioid and propofol–placebo (P<0.001). **Significant difference between propofol–remifentanil plus propofol–alfentanil and propofol–fentanyl (P<0.05)

	Propofol placebo	Propofol fentanyl	Propofol sufentanil	Propofol remifentanil	Propofol alfentanil
BIS_{50}	60.5 (58–63)	69.5 (67.8–71.1)*	66.2 (62.6–69.1)*	74.0 (69.9–78.2)*,†	74.6 (72.9–76.2)*,†
EC_{50} (μg·ml^{-1})	2.34 (2.21–2.46)	1.87 (1.63–2.10)‡,**	1.80 (1.45–2.14)‡	1.60 (1.23–1.96)‡,**	1.65 (1.48–1.82)‡,**

Table 4 Prediction probability (P_k) for loss of consciousness. EC=effect site concentration of propofol. BIS=bispectral index. Values are mean (SD)

	P_k				
	Propofol placebo	**Propofol fentanyl**	**Propofol sufentanil**	**Propofol remifentanil**	**Propofol alfentanil**
BIS	0.954 (0.0018)	0.974 (0.0099)	0.977 (0.0095)	0.967 (0.0085)	0.971 (0.010)
EC	0.982 (0.0064)	0.953 (0.0215)	0.964 (0.016)	0.975 (0.0120)	0.955 (0.0225)

who received an opioid were more sedated at 1 and 2 μg ml^{-1} effect-site concentration of propofol than those receiving a placebo. In all groups, patients lost consciousness before the effect-site concentration of propofol reached 4 μg ml^{-1}. At LOC, BIS values were higher in all 'opioid' groups than those in the placebo group (resulting particularly in higher BIS_{50} values, Table 3).

The effect-site concentration of propofol at LOC was lower in patients given opioids than in those given placebo, resulting in lower EC_{50} values (Table 3). There were statistically significant differences in BIS_{50} and EC_{50} among the opioid groups (Table 3). The P_ks for BIS and EC, which indicate the probability of correctly predicting the LOC with the different drugs, are listed in Table 4.

There was no change in mean arterial pressure when opioids were administered before the propofol. Subsequent administration of propofol significantly reduced mean arterial pressure in all groups (P<0.05). At effect-site concentrations of propofol of 2 and 4 μg ml^{-1}, mean arterial pressure was significantly lower in the opioid groups than in the placebo group (P<0.05). Heart rate did not change significantly throughout the study, except for an increase in the placebo group when the effect-site concentration of propofol was 4 μg ml^{-1}.

Oxygen saturation remained >95% and stable during the procedure. Episodes of apnoea (defined as respiratory arrest for >15 s) were observed in all opioid groups (3/14 with alfentanil, 3/14 with sufentanil, 4/13 with fentanyl and 11/14 with remifentanil) but not in the placebo group. These episodes of apnoea were transitory and responded well to verbal stimulation. None of the patients had to be ventilated before LOC.

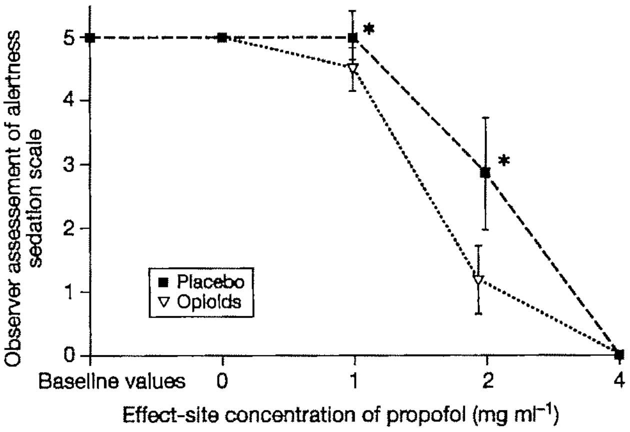

Fig 1 Relationship between Observer Assessment of Alertness/Sedation Scale (OAA/S) and effect-site concentration of propofol. There was a significant difference between placebo and opioids (P<0.05).

Discussion

To our knowledge, this is the first study to compare the effect of four widely used opioids on the sedative and hypnotic effects of propofol in patients during target-controlled induction of anaesthesia. We show that analgesic concentrations of fentanyl, alfentanil, remifentanil or sufentanil facilitate the LOC induced by propofol. That is, patients lost consciousness at lower propofol effect-site concentrations than with a placebo. However, the BIS did not show this increased hypnotic effect, since LOC occurred at a higher BIS_{50} in the presence of an opioid.

In the present study, both EEG and clinical evaluation were used to measure sedation and hypnosis. The BIS is generally considered as a reliable method for measuring the 'state of consciousness',[11] particularly when propofol is administered.[12] The BIS can provide reliable monitoring for sedation, hypnosis or even for predicting LOC, especially when a single drug is used, such as propofol, midazolam, isoflurane[6 18] or sevoflurane.[19]

The administration of opioids together with anaesthetics may substantially change the predictive value of the BIS. As Sebel and colleagues[11] have pointed out, the adjunctive use of an opioid analgesic confounds the use of the BIS as a measure of anaesthetic adequacy when movement response to skin incision is used as the primary endpoint. Sakai and colleagues[20] showed that fentanyl pretreatment potentiated the effect of propofol for achieving the hypnotic endpoint. They found higher BIS and lower propofol concentrations in the propofol + fentanyl group compared with the propofol group at unresponsiveness to verbal commands, loss of eyelash reflex and response to mechanical nasal membrane stimulation. However, others[21] found that remifentanil, when added to propofol, did not affect BIS before stimulation.

Iselin-Chaves and colleagues[9] studied the effect of increasing doses of alfentanil together with propofol on BIS and LOC. They found that alfentanil did not significantly affect BIS_{50} or propofol plasma concentration (Cp_{50}) values required for LOC. However, in a recent study,[22] they clearly showed that alfentanil decreased the propofol concentration required for LOC. Unfortunately, BIS values were not reported.

It is important to emphasize that the results of the present study are based on predicted effect-site concentrations of propofol and opioids. It is well known that propofol pharmacokinetics can be altered by alfentanil[2] and remifentanil.[25] We chose not to measure the plasma concentrations of propofol for two reasons. Firstly, in everyday clinical practice with target-controlled infusion devices, predicted rather than measured plasma and effect-site concentrations are used. Secondly, the target-controlled infusion device is not only readily available commercially, but has been proven to be a reliable method of propofol administration for induction and maintenance of anaesthesia. The analgesic concentrations of opioids used in this study correspond to those usually used during induction of anaesthesia for minor surgery. The results of this study show that addition of an opioid to induction with propofol results in LOC at higher BIS_{50} and lower EC_{50} values. One possible explanation for this may be that opioids, in the analgesic concentrations used in this study, produce minimal electrophysiological alterations on the cerebral cortex. To induce EEG changes, higher concentrations are necessary. Indeed, Shafer and colleagues estimated the IC_{50} (steady-state concentration that produces 50% of the maximal (observed drug effect) of fentanyl at 7.8 ng ml^{-1}, of alfentanil at 480 ng ml^{-1} and of sufentanil at 0.69 ng ml^{-1} for the appearance of EEG depression.[23] Another possible reason why the BIS did not reveal the interaction between propofol and an opioid may be that non-cortical structures that are undetectable by EEG, such as the locus coeruleus, are involved in the mechanism of drug effect.[24]

We found statistically significant differences among the opioid groups (Table 3). There are three possible reasons for this. Firstly, the opioid concentrations used in this study were based on data published in the literature,[23 25] and there is no evidence that the concentrations were equipotent. Secondly, we did not measure plasma concentrations of propofol, so we do not know how the pharmacokinetics of propofol were modified by different opioids. Thirdly, there may be differences in the hypnotic properties among the opioids used in this study.

There is the potential for bias in the assessment of sedation and LOC in the present study because opioids may induce thoracic rigidity or apnoea. This clinical effect of opioids and their analgesic action may interfere with the evaluation of sedation and LOC. The sedation score used here is valid and easy to perform.[26] The OAA/S was evaluated by the same anaesthetist for all patients, to avoid bias. To reduce the influence of interindividual variability in the biophase equilibration of the drugs, all measurements were made at steady-state effect-site concentrations of propofol and opioids.

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Antinociceptive properties of neurosteroids IV: pilot study demonstrating the analgesic effects of alphadolone administered orally to humans

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Fourteen patients scheduled for orthopaedic knee reconstruction surgery were enrolled in a prospective, double-blind, randomized study in which they received alphadolone (25–500 mg, n=9) or placebo (lactose, n=5) given orally 1 h after operation. All the subjects received a standardized general anaesthetic and the same type of surgery followed by physiotherapy using a continuous passive movement machine. Morphine was administered intravenously after operation by patient-controlled analgesia. Verbal rating and visual analogue scores assessed pain experiences for 6 h. Orally administered alphadolone up to 500 mg caused no increase in sedation, respiratory depression, nausea or vomiting. The experiences of these side-effects were all rated as none, mild or moderate. Orally administered alphadolone caused statistically significant reductions in morphine use and simultaneous highly significant reductions in pain scores. We conclude that alphadolone is a useful analgesic in humans when given by the oral route.

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Gamma aminobutyric acid (GABA) is involved with sensory processing throughout the central nervous system, including processing of nociceptive information at the level of the spinal cord.[1] Two major subdivisions of GABA receptors exist, A and B. The GABA$_A$ receptor is a pentameric ligand-gated chloride ion channel with binding sites for GABA and separate modulatory binding sites for barbiturates, benzodiazepines, propofol and neurosteroids.[2 3] Heterogeneity of steroid binding sites on GABA$_A$ receptors has also been suggested.[4] GABA$_A$ receptors are present within the dorsal horn of the spinal cord.[5–7] Some of these may be targeted by intrathecal injection of benzodiazepines to produce spinally mediated antinociception in rats and pain relief in man.[8 9] There is also some evidence that spinal GABA$_A$ receptors may be targeted by inhalational general anaesthetics.[10]

Few articles have been published describing the effect of neuroactive steroids on the spinal cord. One article reported inhibition of spontaneous and evoked electrical activity in spinal cord neurones after intravenous injection of Saffan, a veterinary steroid combination anaesthetic containing alphaxalone 9 mg ml^{-1} and alphadolone 3 mg ml^{-1} dissolved in Cremophor EL.[11] These observations of effects on neuronal activity were not specific for any particular sensory modality. Intrathecal injection of water-soluble aminosteroid anaesthetics has been shown to cause antinociception in rats, which was a result of interaction of the drugs with spinal cord GABA$_A$ receptors.[12] Subanaesthetic doses of Saffan causes powerful antinociception in rats.[13] Further investigations showed that all the sedative and anaesthetic properties of the mixture were due to the alphaxalone content and all of the antinociceptive properties were due to the alphadolone content. Alphadolone caused spinally mediated antinociception by an interaction with spinal cord GABA$_A$ receptors when the drug was given intraperitoneally or intragastrically to rats without any signs of sedation, even when it was given at a very high dose.[14] Therefore, we performed a pilot study to provide initial information on the tolerability and safety of the drug and initial data on its efficacy.

Materials and methods

The local research ethics committee approved the study. This was a small pilot study of dose escalation and proof of concept design, and incorporated some randomization and

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Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Treatment: placebo P or alphadolone A (dose mg)	P	A(25)	A(50)	P	A(100)	A(250)	A(500)	A(250)	P	A(250)	P	P	A(250)	A(250)
Study progress	First part (dose escalation) →							Second part (double blind comparison) →						

Fig 1 Protocol for both parts of the study, showing dose and nature of treatment and the point of conversion from part 1 (dose escalation) to part 2 (comparison of alphadolone 250 mg with placebo).

placebo control because of the nature of the measurements, i.e. pain. The study was randomized, double-blind and placebo-controlled.

The study consisted of two parts, as shown in Fig. 1. At any time during both parts, if the patient was randomized to receive placebo, then a capsule containing lactose 250 mg was administered orally at the time of medication. If the subject was randomized to receive alphadolone, then the first patient so randomized received alphadolone acetate 25 mg orally. The patient was monitored for efficacy of the medication and side-effects. If there were no unacceptable side-effects, such as respiratory depression, severe sedation or disorientation, then the next patient randomized to receive the active treatment received a higher dose. The dose escalation planned was 25, 50, 100, 250, 500 and 1000 mg. The trial switched from the dose escalation phase to the comparison phase when there was clear evidence of efficacy. The senior author (CSG) assessed this and the study switched to part 2 without the observer's knowledge. Patient and observer (AR) remained unaware of the nature of the treatment, whether placebo or alphadolone and what dose.

The randomization led to patients 1, 4, 9, 11 and 12 receiving placebo medication. Patient 2 received alphadolone 25 mg, patient 3 alphadolone 50 mg, patient 5 alphadolone 100 mg, patient 6 alphadolone 250 mg and patient 7 alphadolone 500 mg (Fig. 1).

There seemed to be efficacy with the 100, 250 and 500 mg doses in these patients. Thus, in the second part of the study, a double-blind comparison of placebo with alphadolone 250 mg was carried out. Patients 8, 10, 13 and 14 received alphadolone 250 mg and patients 9, 11 and 12 received placebo.

The protocol below was carried out in all patients in both parts of the study and the data were analysed for the efficacy and side-effect profile of alphadolone compared with placebo.

Protocol

Patients (n=14) scheduled for knee reconstruction surgery gave written informed consent to be included in the study after inclusion and exclusion criteria had been met. Inclusion criteria were: ASA 1–2; age 18–70 yr; not using regular analgesics apart from paracetamol and non-steroidal anti-inflammatory drugs. All analgesic medications were withheld before surgery on the day of surgery. Subjects who had renal, hepatic or respiratory disease (other than mild asthma) and pregnant women were excluded from the study. No epidural, spinal or knee-joint local anaesthetic or opioid injections were allowed. After the patients had given informed consent, they were given an opportunity to familiarize themselves with the patient-controlled analgesia (PCA) machine and to practice completing the visual analogue scale (VAS) and verbal rating scale used for postoperative assessments.

No premedication was given. The patients were taken to the operating theatre and given a standardized anaesthetic that consisted of propofol induction followed by propofol infusion and the muscle relaxant of the anaesthetist's preference. The trachea was intubated and the lungs were ventilated with a mixture of nitrous oxide and oxygen. Incremental doses of morphine (1–2 mg i.v.) were given as indicated by the assessment of the depth of anaesthesia by normal monitoring techniques. The amount of morphine used in the operating theatre was recorded. After surgery, muscle relaxation was reversed with atropine and neostigmine. In the recovery ward, the patient was reintroduced to the PCA machine, which contained morphine and was set to deliver a 1 mg dose with a lockout time of 5 min. The patient was discharged to the ward 30 min later.

Placebo or alphadolone was given orally with 100 ml of water 1 h after return to the ward. The following observations and measurements were made 1 h before, 30 min before and just before giving the test medication, and were repeated every 30 min thereafter until 6 h after the capsule

Table 1 Amounts of morphine administered intravenously to placebo- and alphadolone-treated patients as part of the anaesthetic and postoperative PCA before capsule administration

Treatment	Morphine received before capsule (mg)		
	Mean	**SD**	**Range**
Placebo (n=5)	16.2	4.32	11–26
Alphadolone (n=7)	17.22	3.15	10–21

had been given: *sedation*, on a four-point scale (none, mild, moderate, severe); *nausea* (none, mild, moderate, severe vomiting); *morphine consumption* during the last 30 min; *10 cm VAS for pain* (no pain, most intense pain imaginable); *respiratory depression score* (none=respiratory rate greater than 10 b.p.m., oxygen saturation greater than 95%; mild=respiratory rate greater than 6 and less than 10 b.p.m., and oxygen saturation greater than 95%; moderate= respiratory rate less than 6 b.p.m. but oxygen saturation greater than 95%; severe=respiratory rate less than 6 b.p.m. and/or oxygen saturation less than 95%); *light-headedness* (none=no dizziness; mild=light dizziness but no nystagmus; moderate=feels dizzy and has nystagmus; severe=very dizzy with nausea); *slurred speech* (none, mild, moderate, severe); *presence of confusion or disorientation*; *gaze-evoked nystagmus* (none; mild=1–2 jerks; moderate= constant slow jerks; severe=fast jerks and feeling dizzy); *lack of co-ordination*, with two tests: (i) close eyes, touch nose with finger; (ii) touch fingers 1, 2, 3 and 4 in turn with thumb (classified as none=both tests accomplished; mild= both tests accomplished but slowly; moderate=one test achieved after two attempts; severe=failed both tests after two attempts at each).

One hour after the capsule had been given, all patients commenced physiotherapy with a continuous passive movement (CPM) machine. This machine forcibly moves the knee through an angle of 30° to 45°. Thus, after capsule administration the pain measurements were on movement, whereas before this they were at rest.

All patients had 10 ml of blood taken from a vein immediately before capsule administration and 30 min and 1, 1.5, 2, 3, 4 and 6 h after capsule administration. Blood was placed in heparinized tubes and centrifuged and the plasma was decanted for later analysis of blood alphadolone concentration by the Key Centre for Applied and Nutritional Toxicology, Royal Melbourne Institute of Technology.

Statistics

Statistical tests were applied to the data obtained in part 2 in order to compare the alphadolone and placebo treatment groups. Morphine consumption from the PCA in each half-hour period for the 6 h after drug treatment was classified as 0, 1, 2, 3 or 4 mg. The numbers of times each dose had been used in the placebo- and alphadolone-treated groups were placed in a contingency table and a χ^2 test was applied. The χ^2 test was also used to compare the groups with respect to all other scores except the VAS for pain intensity. The latter measurements at each 30 min period were transformed by dividing them by the mean of the three readings taken before capsule administration. All of the values for the alphadolone-treated group were compared with those for placebo treatment using the Mann–Whitney U-test. In all statistical tests, a P value less than 0.05 was considered to be statistically significant.

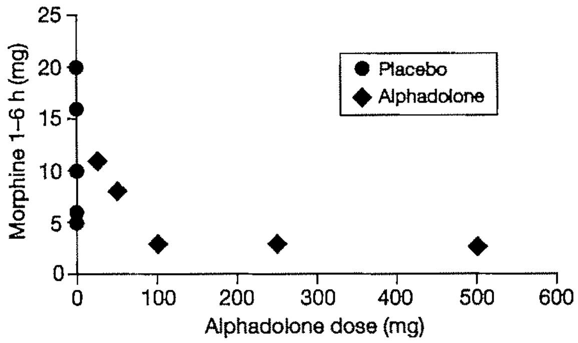

Fig 2 PCA morphine consumption by five placebo-treated patients and the patients who received alphadolone on an escalating scale (25, 50, 100, 250 and 500 mg).

Results

No patient in the study experienced more than mild light-headedness, or any respiratory depression, slurred speech, confusion, disorientation, gaze-evoked nystagmus or lack of co-ordination. In the control group of five patients, there were four males and one female. In the alphadolone group there were nine patients, five males and four females. The ages of the placebo-treated patients were 18, 23, 24, 31 and 61 yr. The ages of the alphadolone group were 18, 19, 23, 24, 24, 26, 28, 29 and 33 yr.

The doses of morphine received by the patients in the operating theatre, recovery ward and ward before capsule administration were not significantly different between placebo- and alphadolone-treated patients (Table 1).

Dose escalation (part 1 of the study)

Morphine consumption from the PCA machine for the first five alphadolone-treated patients (patients 2, 3, 5, 6 and 7) in the 6 h after capsule administration compared with all placebo treated patients is shown in Fig. 2.

The total range of morphine consumption of the five placebo-treated patients is shown at alphadolone dose 0. During the 6 h after capsule administration there was a progressive reduction in morphine use as the alphadolone dose increased from 25 to 100 mg. This was used as a guide to decide the dose of alphadolone to be used in part 2 of the study. Doses of alphadolone 100 mg and above were all associated with PCA morphine use, which was lower than the lowest use by placebo-treated patients.

Table 2 (A) Nausea scores. Patients' experiences were rated on a four-point scale as none, mild, moderate or severe. There were no differences between the treatment groups. There were no cases of severe nausea and vomiting or heavy sedation. The addition of alphadolone to the postoperative medication did not lead to greater sedation, nausea or vomiting. No scores of 3 or 4. P=0.9459 (χ^2 test) (B) Sedation scores. Details as for Table 2A. No scores of 3 or 4. P=0.8661 (χ^2 test)

(A) Treatment	None	Mild	Moderate
Placebo (n=5)	51	8	1
Alphadolone (n=7)	72	10	1

(B) Treatment	None	Mild	Moderate
Placebo (n=5)	14	33	13
Alphadolone (n=7)	20	48	15

On this basis, it was decided to switch the rest of the trial (part 2) to a double-blind comparison of alphadolone 250 mg with placebo in the remaining patients. Data from placebo-treated patients (n=5) and alphadolone-treated patients (100, 250 and 500 mg, n=7) were combined for statistical comparisons.

Sedation and nausea scores

These data were entered into a contingency table (Table 2).

A χ^2 test for nausea score (Table 2A) and sedation score (Table 2B) showed that there were no significant differences between placebo and alphadolone treatment. There were no scores of 3 or 4 for either symptom, and the large majority of patients had either no nausea or sedation or only mild symptoms.

Verbal rating scale for pain

Verbal rating scale scores were entered into a 4×2 contingency table (Table 3). A χ^2 test revealed that the alphadolone-treated patients recorded significantly lower pain scores.

Visual analogue scale

Scores were entered into a spreadsheet and then transformed by dividing by the mean of the three VAS scores measured at the time of capsule administration and 30 min and 1 h before that (Table 4). Thus, each VAS score after capsule administration was expressed as a ratio of the pretreatment readings. The transformed data were then collected for all placebo-treated (n=5) and alphadolone-treated (n=7) patients. These two data sets were placed in two columns and subjected to a Mann–Whitney U-test. There was a significant difference (P=0.0117) between the two groups, the alphadolone patients having significantly lower standardized VAS scores than placebo-treated patients.

Morphine consumption

The morphine dosage was in increments of 1 mg, i.e. one press of the button always delivered 1 mg. All of the 30 min measurements of morphine consumption were 0, 1, 2, 3 or 4 mg. The frequency of occurrence of each of these values were entered into a contingency table (Table 5).

Table 3 Contingency table showing the frequency of scores on the verbal rating scale for pain (no pain, mild, moderate or severe pain) in alphadolone- and placebo-treated patients. Alphadolone treatment led to highly significant reductions in pain rating. P<0.001

Treatment	No pain	Mild pain	Moderate pain	Severe pain
Placebo (n=5)	0	23	30	7
Alphadolone (n=7)	6	53	20	4

It can be seen that the χ^2 test revealed a statistically significant difference (P=0.0153). However, the χ^2 test should not be applied to these data as they stand because the number of observations in the cells relating to morphine 4 mg is so low. If the numbers in the cells relating to morphine 4 mg are added to the 3 mg cells (this only applies to one observation in the placebo group), then the χ^2 test is valid for the data and computation revealed χ^2=12.24997 and P=0.00651.

CPM duration

Each patient was put on the CPM machine 1 h after capsule administration. The patient could be taken off this machine at the discretion of the nursing staff. Thus, little can be made of these data except to rule out the possibility that the alphadolone patients were subjected to knee movements for shorter periods of time.

Table 6 shows that this was not the case.

Alphadolone blood concentrations

Analysis of the blood samples revealed no detectable alphadolone. The lower limit of detection was 50 ng ml^{-1}. However, treatment of the plasma samples with the enzyme glucuronidase revealed that the alphadolone had been absorbed and conjugated to a glucuronide group. Alphadolone metabolite was found in µg ml^{-1} concentrations in the plasma in all the patients treated with alphadolone that were analysed (250 mg, five patients; 500 mg, one patient). In four of these patients the metabolite was detected in the first sample taken after the alphadolone capsule had been given. In all cases the metabolite was still present, although at a lower concentration, at the 6 h sampling time point.

Discussion

Hans Selye showed almost 60 yr ago that steroid hormones given parenterally and orally could produce sedation and anaesthesia.[15] Furthermore, he was able to show that it was possible to produce steroid molecules that were anaesthetics but devoid of hormonal action.[16] The speed of onset of the sedative effects of these compounds was the first observ-

Table 4 VAS readings for pain measured in mm before (Pre) and every 30 min after capsule administration. Each VAS reading taken at each 30 min period after capsule administration (A) .was transformed by dividing it by the mean of the three VAS readings taken 1 h, 30 min and immediately before capsule administration. (B) Standardized VAS scores (standardized ratio of precapsule levels shown in Table 4A. For details see legend to Table 4A). $P<0.05$ (Mann–Whitney *U*-test)

(A) Patient, treatment	Pre	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
1, placebo	30	22	19	13	22	29	30	28	30	27	22	15	9
2, alphadolone 25 mg	42	25	25	35	24	19	13	23	48	27	18	25	50
3, alphadolone 50 mg	70	27	24	53	47	29	25	48	47	47	38	56	77
4, placebo	54	25	25	28	29	27	22	22	22	30	27	22	27
5, alphadolone 100 mg	64	51	32	20		40	34	42	63	68	77	79	88
6, alphadolone 250 mg	32	49	53	45	37	31	10	10	3	15	25	16	30
7, alphadolone 500 mg	63	37	30	43	33	28	45	25	25	24	21	25	21
8, alphadolone 250 mg	61	30	28	32	35	54	20	34	30	42	38	21	20
9, placebo	52	35	62	65	63	42	25	26	28	43	28	54	66
10, alphadolone 250 mg	52	20	35	15	8	55	50	72	89	50	79	48	41
11, placebo	31	29	31	27	25	26	38	35	44	39	34	35	36
12, placebo	27	24	19	34	17	17	13	14	15	26	21	15	13
13, alphadolone 250 mg	41	55	27	18	29	26	25	24	35	20	23	12	22
14, alphadolone 250 mg	59	23	23	9	6	7	6	5	0	0	5	5	3

(B) Patient, treatment	Pre	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
1, placebo	1.00	0.75	0.64	0.44	0.75	0.98	1.02	0.95	1.02	0.92	0.75	0.51	0.31
2, alphadolone 25 mg	1.00	0.60	0.60	0.84	0.58	0.46	0.31	0.55	1.15	0.65	0.43	0.60	1.20
3, alphadolone 50 mg	1.00	0.39	0.34	0.76	0.67	0.42	0.36	0.69	0.67	0.67	0.55	0.80	1.11
4, placebo	1.00	0.46	0.46	0.52	0.54	0.50	0.41	0.41	0.41	0.56	0.50	0.41	0.50
5, alphadolone 100 mg	1.00	0.80	0.50	0.31		0.63	0.53	0.66	0.99	1.07	1.21	1.24	1.38
6, alphadolone 250 mg	1.00	1.53	1.66	1.41	1.16	0.97	0.31	0.31	0.09	0.47	0.78	0.50	0.94
7, alphadolone 500 mg	1.00	0.59	0.48	0.69	0.53	0.45	0.72	0.40	0.40	0.38	0.34	0.40	0.34
8, alphadolone 250 mg	1.00	0.49	0.46	0.52	0.57	0.88	0.33	0.55	0.49	0.68	0.62	0.34	0.33
9, placebo	1.00	0.68	1.20	1.26	1.22	0.81	0.48	0.50	0.54	0.83	0.54	1.05	1.28
10, alphadolone 250 mg	1.00	0.39	0.68	0.29	0.15	1.06	0.97	1.39	1.72	0.97	1.53	0.93	0.79
11, placebo,	1.00	0.94	1.00	0.87	0.81	0.84	1.23	1.13	1.42	1.26	1.10	1.13	1.16
12, placebo	1.00	0.90	0.71	1.27	0.64	0.64	0.49	0.52	0.56	0.97	0.79	0.56	0.49
13, alphadolone 250 mg	1.00	1.35	0.66	0.44	0.71	0.64	0.61	0.59	0.86	0.49	0.57	0.30	0.54
14, alphadolone 250 mg	1.00	0.39	0.39	0.15	0.10	0.12	0.10	0.09	0.00	0.00	0.09	0.09	0.05

Table 5 Contingency table showing the frequency with which the alphadolone- and placebo-treated patients pressed the PCA button in each 30 min period. Alphadolone treatment led to a significant reduction in the frequency of requests for morphine from the PCA machine. $\chi^2=12.280738$; $P=0.01534$

Treatment	Number of requests from the PCA machine in 30 min period				
	0	1	2	3	4
Placebo ($n=5$)	25	18	7	9	1
Alphadolone ($n=7$)	39	29	15	1	0

Table 6 Time spent on the CPM machine (h). No significant difference

	Placebo	Alphadolone
Mean	4.46	7.82
Median	5.00	5.00
Range	3–6	2.25–17

ation that suggested a non-genomic mechanism. The positive modulation of $GABA_A$ receptors as the basis for the sedative, anticonvulsant and hypnotic properties of the neuroactive steroids is now well established.[17–21] Neurosteroid anaesthetic preparations were made following the pioneering work of Selye. These were attractive clinically because of good overall safety, low toxicity and rapid metabolism by the liver, which limited the duration of anaesthetic action.[22–25] They have largely fallen into disuse after the withdrawal of Althesin because of anaphylactoid reactions to the Cremophor EL vehicle.[22 23] Some more recent attempts have been made to make water-soluble neurosteroid anaesthetics.[26 27]

Throughout the development of neurosteroid compounds for use in humans, researchers and developers have concentrated on the hypnotic, sedative and anticonvulsant properties of these compounds.[26–33] Such work has led to the development and patenting of new neurosteroids as anticonvulsants, acting as positive modulators at $GABA_A$ receptors to be used as anti-epileptics[34 35] or for the treatment of migraine.[36] There have been no reports of analgesic or antinociceptive effects of neurosteroids separate from their sedative and anticonvulsant properties. For example, effects on electrically evoked spinal cord neuronal activity after anaesthetic doses of intravenous Althesin (alphaxalone/alphadolone) have been reported.[37 38] Antinociception in animals has been reported after injection of sedative neurosteroids directly into the brain or spinal cord without any control measurements to exclude the effect of sedation on the observations.[39] By contrast, in human experiments, subnarcotic doses of Althesin, like equivalent doses of thiopentone, produced a degree of analgesia during experimental pain elicited by pressure on the tibia.[40–42]. It was found that Althesin alone provided insufficient analgesia for major surgery.[43] It abolished the pain of uterine contractions only during the period of unconsciousness, which was followed by hypersensitivity to pain during recovery.[40 41] There have been observations of gender differences and pregnancy-associated antinociception that have been attributed to steroid hormones.[44–46] All of these compounds caused hormonal effects as well as antinociception. Therefore, apart from data reported by Nadeson and Goodchild,[12–14] selective antinociceptive effects of neurosteroids were not suspected.

Experiments in rats showed that spinal cord GABA$_A$ receptors are responsible for the antinociceptive effects of subanaesthetic doses of propofol[47] and Saffan (alphaxalone/alphadolone mixture).[13] Unexpectedly, it was found that alphadolone was responsible for this antinociception, but only when intraperitoneal or intragastric routes of administration were used.[14] This led to inactivation of the anaesthetic properties of the alphadolone, even when the compound was administered at high doses. This suggested a new use for the neurosteroid as an analgesic and that the active compound might be a metabolite.

This pilot study shows for the first time a number of properties of orally administered alphadolone in humans. Alphadolone is rapidly absorbed after oral administration and metabolized to the glucuronide. It may be well tolerated up to a dose of 500 mg orally, with no observed increase in central nervous system disturbances greater than those caused by hangover of anaesthetic and postoperative medication with morphine. No free alphadolone was detected, which may explain the lack of sedation and is in accordance with the results obtained previously in rats.[13 14] This was followed by a reduced morphine requirement after operation and improved pain scores even in the presence of lower morphine use. This morphine-sparing and improved pain relief occurred in the presence of movement of the joint. Thus, we conclude that orally administered alphadolone may possess useful analgesic properties in humans and that these properties are worthy of more detailed investigation.

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Persistent back pain after spinal anaesthesia in the non-obstetric setting: incidence and predisposing factors

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We determined the incidence of persistent back pain (PBP) after non-obstetrical spinal anaesthesia (SPA) and investigated factors predisposing to such pain in a prospective 1 yr follow-up study in 245 patients undergoing elective general or trauma surgery (218 patients undergoing single SPA, 27 undergoing two to six SPAs). All patients received a first questionnaire 3 months after the last SPA, and those reporting PBP after 3 months were sent a second questionnaire 1 year after the operation. Variables were PBP before and within 5 days, at 3 months and 1 year after SPA, patient satisfaction with SPA, patient characteristics and technical data. Statistical analysis was by contingency tables with Fisher's exact test and an unpaired *t*-test with logistic regression ($P<0.001$ after Bonferroni correction was taken as significant). The response rate in patients who had a single SPA was 56% (122/218). Twenty-three of these 122 patients (18.9%) complained of back pain before SPA compared with 12/122 (10.7%, $P=0.0015$) within 5 days after SPA. After 3 months, 15/122 patients (12.3%) reported PBP with 14 complaining of PBP before SPA ($P<0.0001$), corresponding to an incidence of new PBP of 1/122 (0.8%). Multiple logistic regression revealed that pre-existing back pain was the only variable associated with PBP after 3 months ($P<0.0001$). Patient characteristics and technical factors were not associated with PBP. Nine of the 15 patients with PBP after 3 months returned the second questionnaire: four still reported PBP (three of these had suffered from PBP before SPA). Despite PBP after 3 months, 13/15 patients said they would opt for SPA again. The response rate and results in patients who had had multiple SPAs were similiar to those who had had a single SPA.

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Data on long-term back pain after non-obstetric spinal anaesthesia (SPA) are sparse.[1] As back pain is a relevant public health problem,[2 3] it seems appropriate to evaluate whether or not spinal anaesthesia is associated with persistent back pain (PBP), especially in view of possible public health costs. In addition, concise information regarding PBP after SPA might improve satisfaction with the anaesthetic procedure by improving pre-operative informed consent of the patient. Therefore, we evaluated, in a prospective 1 yr follow-up study, whether spinal anaesthesia is associated with PBP and, if so, which predisposing factors could be identified.

Materials and methods

Within the quality assurance programme of our hospital, all patients scheduled for elective non-obstetric surgery (general, gynecological and orthopaedic surgery) under SPA from January 1 to December 31, 1998 were interviewed using a structured questionnaire.[4] At the pre-operative visit all patients were informed that they would be given a questionnaire 3 months after their operation and were asked to fill out the form completely and return it to the hospital. In addition, for those patients suffering from PBP 3 months after SPA, a second questionnaire was sent 9 months after the first evaluation (i.e. 1 yr after SPA). No other interventions were made.

All patients were premedicated with oral midazolam 7.5 mg 20–30 min before transportation to the operation theatre. In the anaesthetic preparation room, standard monitors (ECG, arterial pressure and oxygen saturation) were applied. Thereafter, an i.v. line (without infusion) was inserted under local anaesthesia and flushed with saline. After infiltration of the L3/4 or L2/3 interspace with 5 ml of 1% mepivacaine (Scandicain; Astra Chemicals, Wedel, Holstein, Germany) SPA was performed with hyperbaric bupivacaine 0.5% (Carbostesin; Astra Chemicals) in the right or left lateral decubitus or in the sitting position using a 24G Sprotte needle in patients aged ≤64 yr (Pajunk GmbH, Geisingen, Germany) or a 22G Quincke needle (Terumo

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Table 1 Patient characteristics and technical data for 122 patients with and without back pain preoperatively ('before SPA'), within 5 days postoperatively and 3 months postoperatively. Data represent mean (SD); SPA=spinal anaesthesia; *P*-value=result of an unpaired *t*-test; *n*=number of patients with and without back pain; the dose of local anaesthestic was rounded to the next 0.5 mg before SPA

	Yes (*n*=23)		No (*n*=99)	Yes (*n*=12)		No (*n*=110)	Yes (*n*=15)		No (*n*=107)
Age (yr)	63 (22–87)		62 (20–93)	59 (22–87)		62 (20–93)	64 (34–87)		61 (20–93)
P-value		0.802			0.500			0.584	
Height (cm)	169 (7)		169 (9)	166 (9)		169 (8)	169 (7)		169 (9)
P-value		0.958			0.206			0.887	
Weight (kg)	71 (12)		75 (13)	72 (17)		74 (12)	71 (12)		75 (13)
P-value		0.219			0.567			0.345	
Duration of anaesthesia (min)				79 (32)		81 (30)	77 (29)		82 (31)
P-value					0.828			0.537	
Duration of operation (min)				36 (22)		38 (20)	32 (23)		39 (20)
P-value					0.669			0.338	
Bupivacaine 0.5% (mg)				12 (2)		14 (2)	13 (2)		14 (2)
P-value					0.009			0.382	
Number of spinal punctures				2 (1.7)		1.5 (1)	1.5 (0.6)		1.6 (1.1)
P-value					0.118			0.747	

Table 2 Gender and presence ('Yes') or absence ('No') of persistent back pain after spinal anaesthesia (SPA) (*n*=122). *P*-values are from Fisher's exact test

Gender	**Back pain**					
	Before SPA		**5 days after SPA**		**3 months after SPA**	
	Yes (*n*=23)	**No (*n*=99)**	**Yes (*n*=12)**	**No (*n*=110)**	**Yes (*n*=15)**	**No (*n*=107)**
Male	12	55	4	63	7	60
Female	11	44	8	47	8	47
P-value		0.818		0.135		0.583

Europe N.V., Leuven, Belgium) in patients aged ≥65 yr.[5] The dose of bupivacaine injected intrathecally depended on the duration of the surgical procedure.[1] During the operation, patients were placed in the supine, left lateral or right lateral decubitus position. In 16 patients, a semi-lithotomy position was used with the hip-ankle angle not less than 90°.

The questionnaire assessed back pain before, within 5 days and 3 months after SPA. Patient satisfaction was evaluated at the end of the questionnaire by asking whether or not the patient would opt for SPA again. We designed the questionnaire specifically to evaluate back pain and not transient neurological symptoms (e.g. unilateral or bilateral pain or dysaesthesia with radiation into buttocks, thighs, calves or legs, as defined by Hampl and colleagues[6]).

Age, gender, height, weight, needle size, interspace punctured, bupivacaine dose, duration of anaesthesia, duration of surgery, and sedation achieved by intravenous injection of midazolam at the patient's request were noted during anaesthesia. All data were stored in a Apple Macintosh computer for later analysis.

All data are presented as means (SD). Categorical data were analysed by means of contingency tables and Fisher's exact test. Continuous variables were evaluated by an unpaired *t*-test. To identify variables associated with PBP after 3 months, multiple logistic regression analysis was carried out with PBP as the dependent variable. After correction for multiple testing (Bonferroni's method) a *P*-value of <0.001 was considered significant.

Results

A total of 285 spinal anaesthetics were performed in 245 patients during the investigation period (218 patients had a single SPA and 27 underwent SPA two to six times).

Single spinal anaesthesia

Patient characteristics are shown in Table 1. No significant difference was found between the patients suffering from back pain before, within 5 days after SPA and 3 months after SPA and those who did not. There was no relationship between the interspace punctured (L2/2, L3/4 or L4/5) and the incidence of PBP after SPA (P=0.3 and 0.4 for PBP after 5 days and 3 months, respectively). There was no relationship between needle size (24G or 22G) and PBP (P=0.12 and 0.27 for PBP 5 days and 3 months after SPA, respectively). Likewise there was no relationship between gender and back pain (Table 2).

Overall, the incidence of back pain was 18.9%, 10.7% and 12.3% before and within 5 days and 3 months after SPA, respectively. There was a strong relationship between back pain before, within 5 days and after 3 months (Table 3): 14 of 15 patients with PBP after 3 months had complained of back pain before SPA (Table 3). Moreover, multiple logistic regression revealed that pre-existing back pain was the only variable associated with PBP after 3 months (P<0.0001, Table 4). Only one patient who had not suffered from back pain before SPA still suffered from back pain after 3

Table 3 Pre-existing back pain and incidence of persistent back pain after spinal anaesthesia (n=122). P-values are the results of χ^2 test followed by Fisher's exact test

	Back pain			
	Before SPA		**5 days after SPA**	
	Yes	**No**	**Yes**	**No**
Back pain				
5 days after SPA				
Yes	7	5	0	0
No	16	94	0	0
P-value	0.0015		0	
3 months after SPA				
Yes	14	1	6	9
No	9	98	6	101
P-value	<0.0001		0.0008	

months. Thus, the incidence of PBP of new onset 3 months after SPA was 1/122 (0.8%).

Overall, 114/122 of the patients (93.5%) were satisfied with the anaesthetic procedure. Of the 15 patients with PBP after 3 months, 13 said they would opt for SPA again. Nine of the 15 patients with PBP after 3 months returned the second questionnaire. Four patients still suffered from back pain; three of these had complained of back pain before SPA. The one patient who complained of new onset of back pain 1 yr after SPA complained also of back pain after 3 months. Seven patients said they would choose SPA again.

Multiple spinal anaesthesia

Twenty-seven patients (nine female) received SPA two to six times. Fifteen of these (56%) returned the first questionnaire. The mean age of the responders was 70 (13) yr. Eleven patients had suffered from back pain before SPA. Three months after the last SPA, only two patients (one female and one male, each of whom had had three spinal anaesthetics) reported back pain; both of them had suffered from back pain before SPA. All 15 patients said they would opt for SPA again. Both patients with PBP after 3 months returned the second questionnaire: both still suffered from back pain; the male patient said he would not opt for SPA again.

Discussion

The main conclusions of this study were as follows: PBP after SPA is almost exclusively associated with pre-existing back pain; new onset of PBP is a rare event; and patient characteristics and technical factors play no significant role.

Our conclusions depend on questioning 245 patients who had undergone 285 spinal anaesthetics for elective general or orthopaedic surgery. Patient questionnaires are an accepted method for evaluating the qualitiy of anaesthetic management and the degree of patient satisfaction with the anaesthetic procedure.[7–9] The response rate, 56%, was comparable to that found by others[8–10] and sufficient for statistical analysis.[11] Our questionnaire, which has been used previously to evaluate PBP after lumbar epidural anaesthesia,[4] was designed specifically to evaluate PBP and not transient neurological symptoms, a syndrome almost specifically associated with the use of hyperbaric lidocaine.[12–20] In addition, hyperbaric 0.5% bupivacaine only marginally, if at all, involved in reports of transient neurological symptoms after SPA.[12–14] Finally, in our questionnaire, patients were asked to report other neurological symptoms or complaints after SPA to take into account possible damage caused by the needle or the position during the operation.

Table 4 Multiple logistic regression analysis of possible variables associated with back pain 3 months after spinal anaesthesia (SPA). Data represent the results of a multiple logistic regression analysis with back pain 3 months after SPA as the dependent variable and the other variables as the independent variables. P-values of <0.001 were considered significant

Variable	**Coefficient**	***t*-value**	***P*-value**
Type of operation	–0.17	–0.94	0.344
Gender	2.33×10^{-3}	0.38	0.97
Age (years)	-3.35×10^{-3}	–1.67	0.096
Height (cm)	-7.57×10^{-4}	–0.2	0.84
Weight (kg)	$-3{,}93\times10^{-4}$	–0.19	0.845
Duration of anaesthesia (min)	1.14×10^{-3}	0.93	0.352
Duration of operation (min)	-7.98×10^{-4}	–0.43	0.662
Vertebral level of puncture	–0.24	–0.47	0.634
Number of spinal punctures	-7.20×10^{-3}	–0.32	0.743
Needle G	–0.41	–1.19	0.236
Dosage of bupivacaine 0.5% (mg)	3.08×10^{-3}	0.23	0.814
Use of midazolam	-8.03×10^{-3}	–0.17	0.861
Back pain			
before	0.55	9.11	<0.0001
5 days after	0.18	2.14	0.034

Since the long-term side effects of a given medical procedure are at least as relevant as those during the hospital stay, we interviewed our patients at least 3 months after the spinal anaesthetic to detect late PBP. Those patients still suffering from back pain 3 months after SPA were sent a second questionnaire to detect PBP after 1 year. We did not use a control group (e.g. those given general anaesthesia for identical types of surgery) in the present study since our main intention was to establish the previously unknown incidence of new onset of PBP after SPA. Since the results obtained in patients with multiple SPA derive from only a small group, we restrict our main conclusions to those patients with single SPA. Therefore, we are confident that our results and conclusions concerning the incidence and predisposing factors of persistent back pain after SPA are valid.

Considering the fact that, in any one year, more than half of the population will suffer from back pain on at least one occasion[3] and that 10–15% of these patients will go on to develop chronic back pain,[2] the problem of PBP after SPA should be discussed with the patient during the preoperative evaluation. Surprisingly, no firm data regarding PBP after SPA exist. Virtually all papers evaluating back pain after

SPA have focused on short-term (post-operative day 1–7) incidence of either transient neurological symptoms[12–19] or back pain[20–30] but not on PBP or the association with pre-existing back pain. The mean incidence of back pain in studies primarily dealing with short-term back pain[20–30] was 15.4% (range: 5.4–29%) which is comparable to the incidence of back pain found in our study, namely 18%, 10.7% and 12.3% before, within 5 days and 3 months after SPA, respectively. This is also comparable to the incidence found in epidemiological data.[2,3] That the number of patients with back pain after spinal anaesthesia was less than those who had back pain before anaesthesia reflects the often transient character of back pain in some of the patients, as described previously.[2,3] Therefore, it is not surprising that 11 and eight patients each who complained of back pain before spinal anaesthesia did not report these complaints 5 days and 3 months after spinal anaesthesia, respectively.

Our study reveals for the first time that the true (new) incidence of PBP is only 0.8% (1/122) 3 months after SPA and that there is a close relationship between back pain before and after SPA. In fact, 14/15 patients with single SPA and 11/15 patients with multiple spinal anaesthetics suffering from PBP after 3 months had complained of back pain before. Thus any conclusions regarding the incidence or aetiology of PBP after SPA are not valid without knowledge of the preoperative status.

The one patient with new onset of PBP after single SPA in our study did not report transient neurological or radicular symptoms,[12–19] so PBP in this patient may have been caused by a flattened lumbar curve secondary to muscle relaxation induced by SPA.[1] However, we cannot exclude the possibility that factors other than SPA may have played a role in the new onset of PBP in this patient.

Our study also shows that most patients do not link their post-operative complaints of low back pain to the spinal anaesthetic. In fact, only two of 15 patients with PBP said they would refuse SPA when operated on again. Moreover, all 15 of the patients who had had multiple spinal anaesthetics said they would opt for SPA again despite persistent low back pain. Thus we believe that it is not justified to deny patients with pre-existing low back pain the benefits of SPA for 'medico-legal' reasons. Rather it seems appropriate to discuss the anaesthetic procedure including the problem of PBP pain pre-operatively more intensively.

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LABORATORY INVESTIGATIONS

Cytochrome P4502B6 and 2C9 do not metabolize midazolam: kinetic analysis and inhibition study with monoclonal antibodies

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We determined the contribution of cytochrome P450 (CYP) isoforms to the metabolism of midazolam by kinetic analysis of human liver microsomes and CYP isoforms and by examining the effect of chemical inhibitors and monoclonal antibodies against CYP isoforms *in vitro*. Midazolam was metabolized to 1′-hydroxymidazolam (1′-OH MDZ) by human liver microsomes with a Michaelis–Menten constant (K_m) of 4.1 (1.0) (mean (SD)) µmol litre^{-1} and a maximum rate of metabolism (V_{max}) of 5.5 (1.1) nmol min^{-1} mg protein^{-1} (n=6). Of the nine representative human liver CYP isoforms, CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5, three (CYP2B6, 3A4 and 3A5) showed midazolam 1′-hydroxylation activity, with K_ms of 40.7, 1.7 and 3.0 µmol litre^{-1}, respectively, and V_{max} values of 12.0, 3.3 and 13.2 nmol min^{-1} nmol P450^{-1}, respectively (n=4). Midazolam 1′-hydroxylation activity of human liver microsomes correlated significantly with testosterone 6β-hydroxylation activity, a marker of CYP3A activity (r^2=0.77, P=0.0001), but not with S-mephenytoin *N*-demethylation activity, a marker of CYP2B6 activity (r^2<0.01, P=0.84) (n=11). Troleandomycin and orphenadrine, chemical inhibitors of CYP isoforms, inhibited the formation of 1′-OH MDZ by human liver microsomes. Monoclonal antibody against CYP3A4 inhibited the formation of 1′-OH MDZ by 79%, whereas monoclonal antibody against CYP2B6 had no effect on midazolam 1′-hydroxylation by human liver microsomes (n=5). These results indicate that only CYP3A4, but not CYP2B6 or CYP2C, is involved in the metabolism of midazolam *in vitro*.

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Midazolam is an intravenous anaesthetic used widely in clinical practice. Numerous studies of the metabolism of midazolam have been performed. Microsomal cytochrome P450 (CYP) 3A in liver is the predominant CYP isoform involved in the metabolism of this agent.[1–3] Metabolism of midazolam is inhibited by concomitantly administered agents such as antimycotics, calcium channel blocking agents and opioids, resulting in significant prolongation of amnesia and disturbance of psychomotor performance.[4–6] Inhibition of CYP3A4 activity by these agents has been considered responsible for inhibiting midazolam metabolism.[4 7] According to a recent *in vivo* and *in vitro* study, propofol decreases the clearance of midazolam by competitively inhibiting CYP3A activity.[8] Since competitive inhibition of one drug by another drug is commonly observed when the two drugs are metabolized by the same CYP isoform,[9] the findings of inhibition of metabolism of midazolam by propofol suggest that the same CYP isoforms may be involved in the metabolism of these anaesthetics. Several lines of evidence, however, have shown that propofol is metabolized predominantly by CYP2B6 or CYP2C9, and that CYP3A4 does not metabolize propofol (Y.Oda, personal communication and ref. [10]), suggesting that CYP2B6 and/or 2C9 as well as CYP3A4 may be involved in the metabolism of midazolam. According to a recent study,[11] both midazolam 1′-hydroxylation activity and immunoquantified CYP3A4 levels significantly correlated with CYP2B6 level in human liver microsomes,

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suggesting that genetic expression of CYP2B6 and CYP3A4 is related, and that CYP2B6 contributes to the metabolism of midazolam.

Although there have been several studies of the metabolism of midazolam by CYP isoforms,[2 7 11] few studies have compared the metabolism of midazolam by CYP2B6 and 2C9 with that by other CYP isoforms, possibly because the human liver contains less of these CYP isoforms than other isoforms.[11 12] CYP isoforms belonging to the CYP2B and 2C families are involved in the metabolism of various agents and are inducible by commonly used agents such as barbiturates and steroids.[13] In addition, the pharmacokinetics of agents metabolized by CYP2B and 2C are significantly influenced by the levels of these isoforms in liver microsomes,[14 15] suggesting that examination of the roles of CYP2B6 and 2C9 in the metabolism of midazolam may shed light on the pharmacokinetic interactions of midazolam with other agents, as well as for testing the possibility of induction and inhibition of metabolism of midazolam by various agents. The objective of this study was to determine the contribution of CYP isoforms including CYP2B6 and 2C9 to the metabolism of midazolam *in vitro* by kinetic analysis and by examination of the effects of chemical inhibitors and monoclonal antibodies on the metabolism of midazolam by liver microsomes.

Materials and methods

Materials

The experimental protocol was approved by the Institutional Human Investigational Committee of Osaka City University Medical School. Midazolam and its metabolites, 1′-hydroxymidazolam (1′-OH MDZ), 4′-hydroxymidazolam (4′-OH MDZ) and 1′,4′-hydroxymidazolam (1′,4′-OH MDZ), were kind gifts from Hoffmann-La Roche Ltd (Nutley, NJ, USA). Testosterone, 6β-hydroxytestosterone, *S*-mephenytoin and its *N*-demethylated metabolite, nirvanol, were obtained from Ultrafine Chemicals (Manchester, UK). Troleandomycin and orphenadrine were obtained from Sigma Chemical Co. (St Louis, MO, USA). Human liver microsomes were obtained from the International Institute for the Advancement of Medicine (Scranton, PA, USA). These microsomes were prepared from liver samples of kidney donors by differential centrifugation; the protein content was measured using Lowry's method,[16] with bovine serum albumin as standard. P450 content was determined from the differential spectrum of carbon monoxide-reduced versus oxidized microsomes as described by Omura and Sato.[17] Specific contents of P450 in human liver microsomes were 0.33–0.66 nmol mg protein^{-1}. Recombinant human P450s expressed in human lymphoblast cells with cytochrome P450 reductase were obtained from Gentest (Woburn, MA, USA). These P450s were supplied as microsomes. Monoclonal antibodies against CYP3A4 and 2B6 were obtained from Gentest. The selectivity and inhibitory activity of these antibodies were confirmed as described in the manufacturer's instructions. In our preliminary experiments, monoclonal antibody against CYP2B6 inhibited *S*-mephenytoin *N*-demethylation by human liver microsomes by 75% at 1.0 mg IgG (mg of microsomal protein)$^{-1}$ and midazolam 1′-hydroxylation by recombinant CYP2B6 by 85% at 0.5 mg IgG (mg of microsomal protein)$^{-1}$. Reduced nicotinamide adenine dinucleotide phosphate (NADPH) was obtained from the Oriental Yeast Co. (Tokyo, Japan). C18 columns (TSK gel ODS-120T, 4.6×150 mm) were obtained from Tosoh Corp. (Tokyo, Japan). Other reagents and organic solvents were from Wako Pure Chemical Industries (Osaka, Japan).

Assay of midazolam metabolism

The metabolism of midazolam by liver microsomes from six individuals was measured as reported previously.[7] There was 100 μg of microsomal protein in each 500 μl incubation mixture. When metabolism of midazolam was measured with each of the CYP isoforms, CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5, 30 pmol of P450 was used instead of human liver microsomes (n=4). The midazolam concentration was between 0.2 and 20 μmol litre^{-1}. Incubation times were 2 and 10 min for experiments with microsomes and CYP isoforms, respectively. The P450 chemical inhibitors, orphenadrine and troleandomycin, were used at a concentration of 100 μmol litre^{-1}, which is sufficient to suppress >80% of CYP2B and CYP3A activities in human liver microsomes.[7 18 19] The Michaelis–Menten constant (K_m) and maximum rate of metabolism (V_{max}) for the formation of 1′-OH MDZ from midazolam were determined by linear regression from Lineweaver–Burk double-reciprocal plots. When antibodies against CYP isoforms were used, microsomes and antibodies were preincubated in test tubes at room temperature for 20 min, followed by addition of midazolam and NADPH. The metabolites were extracted and measured by high-performance liquid chromatography (HPLC) as previously reported.[7] The lower limit of quantification of 1′-OH MDZ, 4′-OH MDZ and 1′,4′-OH MDZ was 20 nmol litre^{-1}. Intra-assay and inter-assay coefficients of variations were <4.8% and 7.0%, respectively.

Assay of S-mephenytoin N-demethylation and testosterone 6β-hydroxylation

S-Mephenytoin *N*-demethylation and testosterone 6β-hydroxylation activities of human liver microsomes from 11 individuals were determined as measures of CYP2B6 and 3A4 activities, respectively, following the method described previously.[11 20] *S*-mephenytoin and testosterone were used at 1 mmol litre^{-1} and 500 μmol litre^{-1}, respectively; these concentrations were chosen based on previously reported K_m values.[20 21] The content of microsomal protein was 400 mg litre^{-1} and incubation time was

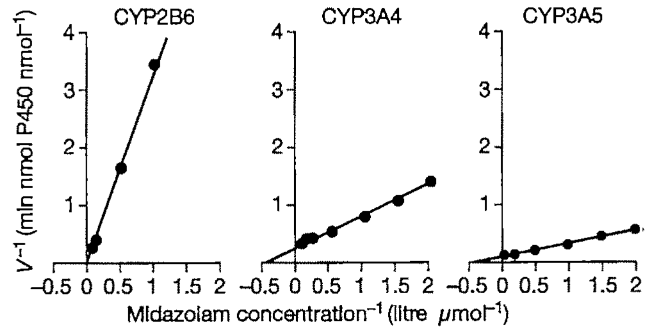

Fig 1 Lineweaver–Burk plots of midazolam 1′-hydroxylation by recombinant CYP2B6, 3A4 and 3A5. Midazolam (0.5–20 μmol litre^{-1}) was incubated at 37°C for 10 mins with recombinant P450 (30 pmol) and 0.4 mmol litre^{-1} reduced NADP in 0.1 mol litre^{-1} potassium phosphate buffer (pH 7.4) in a final volume of 500 μl. Each plot depicts the mean of four experiments.

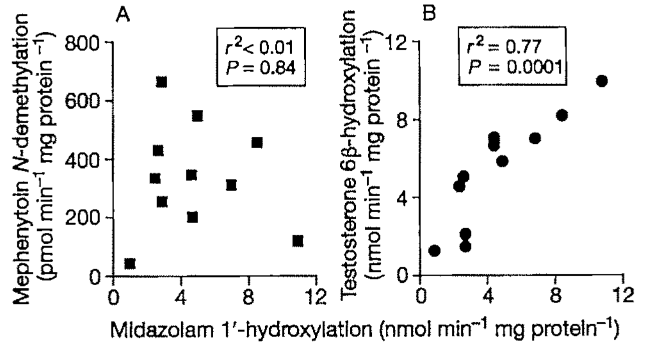

Fig 2 Correlations between midazolam 1′-hydroxylation and *S*-mephenytoin *N*-demethylation, a marker of CYP2B6 activity (A) and testosterone 6β-hydroxylation, a marker of CYP3A4 activity (B) with human liver microsomes obtained from 11 individuals. Concentrations of midazolam, *S*-mephenytoin and testosterone were 10 μmol litre^{-1}, 1 mmol litre^{-1} and 500 μmol litre^{-1}, respectively. Each plot is the mean of three experiments.

20 min for both substrates. The lower limit of detection of nirvanol and 6β-hydroxytestosterone was 50 nmol litre^{-1} and 1 μmol litre^{-1}, respectively. Correlations between midazolam 1′-hydroxylation and *S*-mephenytoin *N*-demethylation and testosterone 6β-hydroxylation activity were determined by linear regression analysis using Statview J version 4.5 (Abacus Concepts, Inc., Berkley, CA, USA). All values are presented as mean (SD); $P<0.05$ was considered statistically significant.

Results

Metabolism of midazolam by human liver microsomes and CYP isoforms

When midazolam was incubated with human liver microsomes, 1′-OH MDZ was the only metabolite detected by HPLC. The total amount of residual midazolam and 1′-OH MDZ formed in the incubation mixture was approximately equal to the total amount of midazolam added to the reaction, suggesting that 1′-OH MDZ was the predominant midazolam metabolite. Rates of formation of 1′-OH MDZ were linear up to 15 and 30 min for the substrate concentrations used with microsomes and P450s, respectively. Single-phase straight curves were obtained from the Lineweaver–Burk plots for 1′-hydroxylation of midazolam by microsomes, with a mean K_m and V_{max} of 4.1 (SD 1.0) μmol litre^{-1} and 5.5 (1.1) nmol min^{-1} mg protein^{-1}, respectively (n=6). These values are comparable to those reported previously.[1 3 7] Of the nine representative CYP isoforms examined, only CYP2B6, 3A4 and 3A5 catalysed midazolam 1′-hydroxylation at a substrate concentration of 10 μmol litre^{-1}. The mean rates of formation of 1′-OH MDZ by CYP2B6, 3A4 and 3A5 were 2.6 (0.7), 2.6 (0.3) and 10.2 (0.6) nmol min^{-1} nmol P450^{-1}, respectively (n=4). CYP2B6 had midazolam metabolic activity comparable to that of CYP3A4, suggesting that CYP2B6 may contribute to the metabolism of midazolam by human liver microsomes.

The K_ms of CYP2B6, 3A4 and 3A5 for midazolam 1′-hydroxylation were 40.7, 1.7, 3.0 μmol litre^{-1}, respectively, and the corresponding V_{max} values were 12.0, 3.3, 13.2 nmol min^{-1} nmol P450^{-1}, respectively (n=4) (Figure 1). These values were obtained from Lineweaver–Burk plots showing the correlation between the reciprocal concentration of midazolam and the mean formation rates of 1′-OH MDZ obtained in four different experiments. K_m values for CYP3A4 and 3A5 were comparable to those obtained with human liver microsomes. The V_{max} for CYP3A5 was higher than that for CYP3A4; however, CYP3A5 is found in only 20–30% of adult human livers, indicating that the contribution of CYP3A5 to midazolam 1′-hydroxylation in liver microsomes is small.[13] Both K_m and V_{max} for CYP2B6 were higher than those for CYP3A4.

Correlation of midazolam 1′-hydroxylation activity with S*-mephenytoin* N*-demethylation and testosterone 6β-hydroxylation activities*

There was 13-fold variation between individuals in the midazolam 1′-hydroxylation activity of human liver microsomes obtained from 11 individuals at a substrate concentration of 10 μmol litre^{-1}. Preliminary studies indicated that the rates of formation of nirvanol from *S*-mephenytoin (1 mmol litre^{-1}) and of 6β-hydroxytestosterone from testosterone (500 μmol litre^{-1}) were linear for ≤1.0 h incubation when microsomal protein content was 400 mg litre^{-1} and for ≤2.0 g litre^{-1} microsomal protein when the incubation time was 20 min. The mean *S*-mephenytoin *N*-demethylation and testosterone 6β-hydroxylation activity of human liver microsomes was 339 (185) pmol min^{-1} mg protein^{-1} and 5.4 (2.5) nmol min^{-1} mg protein^{-1}, respectively. These values were comparable to those reported previously.[20 21] There was a significant correlation between midazolam 1′-

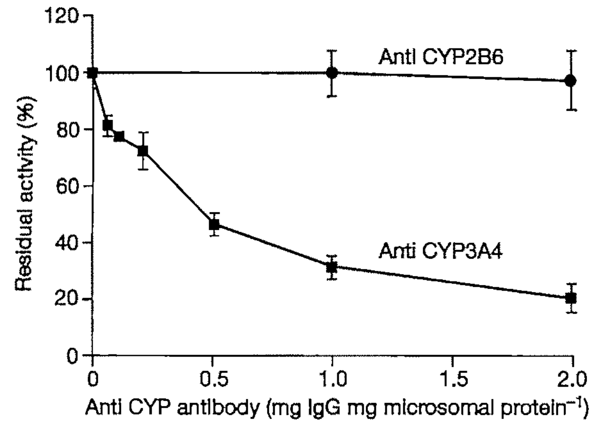

Fig 3 Effects of monoclonal antibodies against CYP2B6 and 3A4 on midazolam 1′-hydroxylation. Human liver microsomes (100 μg of protein) obtained from five individuals were preincubated with antibodies at room temperature for 20 min followed by incubation with midazolam (10 μmol litre^{-1}) and reduced NADP (0.4 mmol litre^{-1}) in 0.1 mol litre^{-1} potassium phosphate buffer (pH 7.4) at 37°C for 2 min in a final volume of 500 μl. Midazolam 1′-hydroxylation activity without antibodies was 6.8 (2.0) nmol min^{-1} mg protein^{-1}. Each plot depicts the mean±SD of five experiments.

hydroxylation and testosterone 6β-hydroxylation, a marker of CYP3A4 activity (r^2=0.77, P=0.0001), whereas no correlation was found between midazolam 1′-hydroxylation and *S*-mephenytoin *N*-demethylation, a marker of CYP2B6 activity (r^2<0.01, P=0.84) (Figure 2).

Inhibition of midazolam metabolism by orphenadrine, troleandomycin and monoclonal antibodies

Both orphenadrine, an inhibitor of CYP2B6, and troleandomycin, an inhibitor of CYP3A4, inhibited the formation of 1′-OH MDZ from midazolam (10 μmol litre^{-1}) by human liver microsomes by 54 (3.6)% and 95 (0.8)%, respectively (n=6). Monoclonal antibody against CYP3A4 inhibited the formation of 1′-OH MDZ from midazolam (10 μmol litre^{-1}) by human liver microsomes by 79 (5.1)%, whereas antibody against CYP2B6 had no effect (n=5) (Figure 3). Since the results obtained with antibodies are not consistent with those obtained with chemical inhibitors of CYP isoforms, chemical inhibitors of CYP isoforms were added to the reaction mixture containing CYP2B6 or 3A4 to elucidate the specificities of those chemical inhibitors to each CYP isoform at a midazolam concentration of 10 μmol litre^{-1}. Troleandomycin completely inhibited the formation of 1′-OH MDZ by CYP3A4 and decreased the formation of 1′-OH MDZ by CYP2B6 by 26 (range 22–30)%. Orphenadrine decreased the formation of 1′-OH MDZ by CYP2B6 by 67 (range 65–68)% and that by CYP3A4 by 62 (range 60–66)% (mean of three experiments). These results demonstrated that orphenadrine inhibits CYP3A4 as well as CYP2B6 activities and is not a selective inhibitor of CYP2B6.

Discussion

In this study, we have shown that neither CYP2C9 nor 2C19 metabolizes midazolam, consistent with the findings of our previous study.[7] Of the representative CYP isoforms in liver, CYP2B6 as well as 3A4 and 3A5 had midazolam 1′-hydroxylation activity. However, the K_m value for midazolam 1′-hydroxylation by CYP2B6 was approximately 10-fold that with microsomes and CYP3A4. Midazolam 1′-hydroxylation activity of microsomes correlated significantly with testosterone 6β-hydroxylation, a specific marker of CYP3A4, but not with *S*-mephenytoin *N*-demethylation, a specific marker of CYP2B6. Antibody against CYP2B6 had no effect on midazolam metabolism with human liver microsomes. These results suggest that CYP2B6 is not involved in the metabolism of midazolam. CYP isoforms which metabolize a substrate do not always contribute to the metabolism of the substrate by microsomes or *in vivo*. These findings have been reported previously.[22] According to one study,[11] CYP2B6 has midazolam 1′-hydroxylation activity and a correlation exists between midazolam 1′-hydroxylation and *S*-mephenytoin *N*-demethylation activity, suggesting coregulation of CYP2B6 and 3A4 activities in microsomes. In the present study, however, no relationships were found between CYP2B6 and 3A4 activities, although the reason for this is not clear. Our study also suggests that competitive inhibition of the metabolism of two substrates, such as midazolam and propofol, does not always imply that these two substrates are metabolized by the same CYP isoforms.

Antibody against CYP3A4 inhibited midazolam 1′-hydroxylation by approximately 80%. Orphenadrine has been used as a chemical inhibitor of CYP2B6.[19] In this study, however, orphenadrine inhibited midazolam 1′-hydroxylation by CYP3A4 as well as that by CYP2B6. Orphenadrine could have inhibited the metabolism of midazolam by inhibiting CYP3A4 activity, and not by inhibiting CYP2B6 activity. These results suggest that orphenadrine lacks specificity as a selective CYP2B6 inhibitor at 100 μmol litre^{-1}. To determine the involvement of CYP2B6 in metabolism of a substrate, inhibition studies with characterized antibodies or examination of the correlation of metabolic ratios with typical substrates of CYP2B6 such as *S*-mephenytoin *N*-demethylation and 7-ethoxytrifluoromethylcoumarin would be required.[21]

In conclusion, midazolam is selectively metabolized by CYP3A4, but neither CYP2B6, 2C9 nor 2C19 is involved in the metabolism of midazolam *in vitro*.

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Naloxone improves functional recovery of myocardial stunning in conscious dogs through its action on the central nervous system

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This study tests the hypothesis that naloxone, but not its quarternary salt, naloxone methiodide (which does not enter the central nervous system), improves recovery from myocardial stunning in conscious dogs. Twenty dogs were chronically instrumented for measurement of heart rate, left atrial, aortic and left ventricular pressure (LVP), LV $dP{\cdot}dt_{max}^{-1}$ and myocardial wall thickening fraction (WTF). Regional myocardial blood flow was determined with coloured microspheres. Occluder around the left anterior descending artery (LAD) allowed induction of reversible LAD ischaemia. Each of the 20 dogs underwent two LAD ischaemic challenges. Experiments (performed on separate days, in crossover fashion) were: (i) 10 min of LAD occlusion after application of naloxone 63 μg kg^{-1} or naloxone methiodide 63 μg kg^{-1} and (ii) occlusion without naloxone or naloxone methiodide. WTF was measured at baseline and until complete recovery occurred. LAD ischaemia significantly reduced LAD WTF with (mean (SD) 54 (15)% lower than baseline) and without naloxone (55 (16)% lower than baseline), without significant haemodynamic differences. Between 1 to 30 min of reperfusion, WTF was significantly higher with naloxone (P<0.05). There was no difference in WTF with or without naloxone methiodide. We conclude that naloxone improved recovery from myocardial stunning in conscious dogs, and that this was centrally mediated.

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Keywords: heart, contractility; blood, flow, regional; blood, reperfusion; heart, ventricular function; antagonists opioid

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Endogenous opioid peptides (EOPs) have important roles in cardiovascular regulation and are released upon myocardial ischaemia.[1] There are three major families of EOPs: dynorphin (derived from pre-proenkephalin B), endorphins (derived from pre-pro-opiomelanocortin) and enkephalins (derived from pre-proenkephalin A). The effects of EOPs are probably mainly mediated by opioid receptors.[2] Pharmacological studies have led to the proposal of five classes of opioid receptor (μ, δ, κ, σ and ε), but the pharmacological effects of each receptor type are not completely defined and this classification has been questioned. It remains unclear if EOPs contribute to myocardial stunning, a clinically relevant phenomenon in patients with coronary artery disease or those undergoing cardiac surgery. Myocardial stunning is a general term for the mechanical dysfunction that persists after reperfusion even in the absence of irreversible damage and despite the return of normal, near-normal or supranormal perfusion.[3–5]

The present investigation tests the hypothesis that naloxone, a non-selective opioid receptor antagonist that enters the central nervous system,[6] reduces the severity and duration of myocardial stunning in an experimental model of reversible myocardial ischaemia. Control studies were performed with naloxone methiodide, which does not cross the blood–brain barrier.[6]

Methods

This investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication no. 85-23, revised 1996) and was approved by the District Government of Münster. After overnight fasting, 20 mongrel dogs (10 male and 10 female, weight 24–28 kg) received intramuscular premedication with piritramide 1 mg kg^{-1} and ketamine 5 mg kg^{-1}. The animals were anaesthetized intravenously

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Table 1 Arterial blood pressure (ABP), left atrial pressure (LAP), rate of increase in left ventricular pressure (LV $dP\ dt_{max}^{-1}$), heart rate (HR) and blood flow velocity in the left anterior descending coronary artery (BFV LAD) for the control and naloxone groups at baseline, during ischaemia and at predetermined time points during reperfusion. Data are presented as mean (SD).*Significantly different from baseline. #Significantly different from control

Variable	Experiment	BL	Ischaemia (5 min after occlusion)	Reperfusion								
				1 min	5 min	10 min	30 min	3 h	6 h	12 h	24 h	48 h
ABP	control	132 (38)	126 (16)	122 (19)	125 (16)	124 (16)	122 (16)	120 (22)				
(mm Hg)	naloxone	123 (32)	113 (35)	128 (60)	122 (57)	127 (47)	119 (38)	109 (54)				
LAP	control	1.7 (4)	6.2 (9)*	2.6 (4)	2.1 (5)	1.9 (4)	1.6 (4)	1.8 (3)				
(mm Hg)	naloxone	2.1 (6)	7.3 (12)*	2.5 (5)	1.9 (4)	1.6 (2)	1.4 (3)	2.3 (4)				
LV $dP\ dt^{-1}$	control	1162 (813)	994 (595)	1044 (569)	1045 (693)	1013 (582)	1041 (424)	1039 (784)				
(mm Hg s^{-1})	naloxone	1384 (1379)	1466 (1129)#	1444 (810)#	1374 (680)#	1436 (762)#	1437 (702)#	1525 (1837)				
HR	control	91 (14)	111 (24)*	115 (7)*	101 (20)*	103 (34)*	96 (37)	93 (19)	90 (27)	96 (20)	88 (13)	93 (22)
(beats min^{-1})	naloxone	92 (12)	109 (10)*	117 (29)*	98 (22)	93 (31)	95 (41)	91 (39)	88 (34)	85 (23)	86 (30)	89 (41)
BFV LAD	control	5.6 (2.8)	0*	11.2 (11.1)*	9.5 (5.4)*	6.8 (8.2)	5.9 (4.4)	6.1 (5.4)	5.1 (1.9)	5.2 (2.8)	5.5 (5.7)	4.9 (5.1)
(kHz)	naloxone	5.3 (4.4)	0*	13.2 (9.2)*	10.5 (7.3)*	9.8 (7.6)*	6.9 (5.4)	5.4 (2.8)	5.3 (2.2)	5.5 (3.8)	5.1 (1.3)	5.7 (2.2)

with propofol 5 mg kg^{-1}. After tracheal intubation, anaesthesia was maintained with isoflurane in a mixture of oxygen (35–40%) in air. Perioperative antibiotic prophylaxis was achieved with cefamandole 30 mg kg^{-1}. Details of the instrumentation methods have been published before.[7] Briefly, a left thoracotomy was performed in the fifth intercostal space under aseptic conditions. Eighteen-gauge catheters were inserted into the descending aorta and the left atrium for pressure measurement, injection of microspheres, naloxone and naloxone methiodide, and withdrawal of blood. A pressure microtransducer (Janssen Pharmaceutica, Beerse, Belgium) was inserted into the left ventricle through an apical stab wound to measure left ventricular pressure (LVP). Pulsed Doppler blood flow velocity probes (20 MHz; Baylor College of Medicine, Houston, TX, USA) were fitted around the left anterior descending coronary artery (LAD). To measure the regional myocardial wall thickening fraction (WTF), 10 MHz pulsed Doppler crystals were sutured to the myocardium in the LAD-perfused areas. Proximal to the Doppler flow probe, a pneumatic occluder was positioned around the LAD (proximal to the first main diagonal branch) to induce reversible brief ischaemic episodes in the LAD-perfused myocardium. After closure of the thorax, all leads were tunnelled subcutaneously and exteriorized between the scapulae. After instrumentation, the animals were trained daily to accustom them to the experimental environment and to ensure that they could lie quietly in the cage when connected to the data acquisition system. Aortic and left atrial pressures were measured using disposable pressure transducers. Pressure, flow velocity and wall thickening signals were processed using a six-channel pulsed Doppler system (Baylor College of Medicine). The left ventricular micromanometer was calibrated to pressures measured in the aorta and left atrium. The LVP signal was differentiated electronically (Gould Inc., Cleveland, OH, USA) and all signals were digitally recorded. Experiments were not conducted until the animals had recovered completely from instrumentation and until blood gas and haemodynamic variables were in the normal range. This took 7–10 days after surgery.

Each of the 20 dogs was given two ischaemic challenges, one with no pretreatment and the other with either naloxone (Curamed Pharma Karlsruhe, Germany) or naloxone methiodide (Sigma-Aldrich Chemie, Deisenhofen, Germany)[8] 63 µg kg^{-1} i.v. 5 min before ischaemia. Ten animals received their first coronary artery occlusion without pretreatment. Baseline values were measured in the awake state, 10 min of LAD ischaemia was induced and WTF was monitored until complete recovery occurred. The other 10 animals received naloxone or naloxone methiodide before their first ischaemia to elucidate the site (central or peripheral) of action. In this group, baseline values were measured in the awake state, naloxone 63 µg kg^{-1} or naloxone methiodide 63 µg kg^{-1} was given before induction of 10 min of LAD ischaemia and WTF was monitored until complete recovery occurred.

A second ischaemic episode was only induced when there was complete recovery of regional myocardial function in the LAD-perfused area; the minimum time interval between the two experiments was 72 h. Regional myocardial blood flow was measured using coloured microspheres (Triton Technology, San Diego, CA, USA). For each measurement, 9×10^6 microspheres suspended in a volume of 3 ml were injected into the left atrium. The reference blood sample was withdrawn from the aortic catheter at a rate of 10 ml min^{-1}. Animals were killed after complete recovery of WTF, after the last ischaemic episode. The heart was dissected and three tissue samples were obtained from the LAD-perfused left ventricle in each dog. LAD samples were taken from the immediate vicinity of the wall thickening probes. Only samples from animals with severe ischaemic dysfunction, as determined by the wall thickening probe, were included. Samples were further dissected into the subendocardial, subepicardial and mid-myocardial layers. Measurement of microspheres in the tissue samples was performed as described previously.[9] Measurement of regional myocardial blood flow to the regions described was carried out four times during the experiment, as follows: (i) without naloxone/naloxone methiodide and without ischaemia (control); (ii) without naloxone/naloxone

Table 2 Arterial blood pressure (ABP), left atrial pressure (LAP), rate of increase in left ventricular pressure (LV $dP\ dt_{max}^{-1}$), heart rate (HR) and blood flow velocity in the left anterior descending coronary artery (BFV LAD) for the control and naloxone methiodide groups at baseline, during ischaemia and at predetermined time points during reperfusion. Data are presented as mean (SD). *Significantly different from baseline. $^{\#}$Significantly different from control

Variable	Experiment	BL	Ischaemia (5 min after occlusion)	Reperfusion								
				1 min	5 min	10 min	30 min	3 h	6 h	12 h	24 h	48 h
ABP (mm Hg)	control	128 (41)	127 (19)	124 (25)	127 (22)	125 (19)	123 (13)	124 (28)				
	naloxone methiodide	125 (28)	123 (22)	126 (38)	124 (28)	125 (32)	121 (41)	122 (22)				
LAP (mm Hg)	control	2.2 (4)	7.4 (12)*	2.3 (4)	2.0 (5)	2.1 (5)	1.9 (6)	2.1 (6)				
	naloxone methiodide	2.3 (5)	7.2 (11)*	2.2 (4)	2.4 (6)	1.9 (5)	2.3 (5)	2.4 (5)				
LV $dP\ dt^{-1}$ (mmHg s^{-1})	control	1255 (1027)	907 (857)	1131 (803)	1199 (879)	1274 (648)	1172 (566)	1185 (730)				
	naloxone methiodide	1289 (1255)	935 (917)	1204 (617)	1041 (813)	1175 (911)	1297 (920)	1226 (927)				
HR (beats min^{-1})	control	93 (21)	114 (27)*	116 (11)*	95 (29)	97 (21)	94 (27)	96 (33)	92 (38)	94 (27)	90 (23)	91 (16)
	naloxone methiodide	90 (16)	112 (23)*	118 (22)*	97 (30)	96 (34)	91 (25)	95 (20)	90 (38)	87 (22)	91 (15)	92 (15)
BFV LAD (kHz)	control	6.3 (3.8)	0*	12.5 (13)*	10.3 (7.0)*	7.5 (15.2)	7.2 (8.9)	6.5 (4.1)	6.6 (2.8)	5.9 (4.1)	5.6 (8.5)	5.7 (5.7)
	naloxone methiodide	5.9 (5.1)	0*	12.8 (10.1)*	10.9 (6.0)*	6.8 (10.8)	7.1 (13.3)	6.2 (8.9)	6.2 (6.0)	5.7 (5.4)	5.5 (2.5)	6.0 (8.2)

methiodide and with ischaemia; (iii) with naloxone/naloxone methiodide and without ischaemia; and (iv) with naloxone/naloxone methiodide and with ischaemia.

Experiments were conducted in chronically instrumented conscious dogs to avoid the effects of acute surgical trauma, anaesthesia, volume and ionic imbalances, and temperature on recovery from stunning. Since multiple stun manoeuvres may induce extensive development of coronary collaterals, precluding the induction of postischaemic dysfunction, the number of ischaemic episodes was restricted to two in each animal.

Statistical analysis

Data were analysed using repeated-measures two-way analysis of variance followed by Bonferroni-corrected Student's t-test whenever appropriate; $P<0.05$ was regarded as significant. Data are presented as mean (SD).

Results

None of the animals had to be excluded from the analysis due to insufficient dysfunction. The maximum degree of regional ischaemic dysfunction was similar during the first and the second ischaemic episodes in each dog.

Blood pressure, heart rate, left atrial pressure and LV dP dt⁻¹

There were no significant changes in arterial blood pressure in either group during or after ischaemia (Tables 1 and 2). Left atrial pressure and heart rate during LAD ischaemia increased significantly in both groups, but there was no significant difference in these variables between the two groups during or after ischaemia. Induction of regional ischaemia did not produce a significant change in LV $dP\ dt_{max}^{-1}$ (Tables 1 and 2). After naloxone administration, LV $dP\ dt_{max}^{-1}$ was significantly higher than in the controls during ischaemia and until 30 min of reperfusion (Table 1). Results with naloxone methiodide were the same as those with controls (Table 2).

Blood flow velocity in the LAD

Blood flow velocity in the LAD-perfused area in the experimental groups was not significantly different from baseline values. During LAD occlusion, LAD flow velocity decreased to zero and increased to values significantly higher than baseline for the first 10 min during reperfusion. There were no significant differences between the experimental groups in flow velocities in the LAD during reperfusion (Tables 1 and 2).

Regional myocardial wall thickening

The WTF in the LAD-perfused area is shown in Figure 1A and B for the naloxone and naloxone methiodide group, respectively. In all animals, severe myocardial dysfunction occurred during LAD ischaemia. Induction of regional ischaemia led to a significant reduction in WTF to negative values (wall thinning) in both experimental conditions; in the presence (mean (SD) 54 (15)% lower than baseline) or absence of naloxone (55 (16)% lower than baseline), and in the presence (57 (25)% lower than baseline) or absence of naloxone methiodide (56 (19)% lower than baseline). After reperfusion, WTF recovered significantly more quickly only in the group receiving naloxone at time points between 1 min and 30 min of reperfusion (92 (9)% vs 25 (46) at 1 min; 100 (5)% vs 37 (54)% at 5 min; 97 (5)% vs 42 (47) at 15 min; 95 (10)% vs 49 (34)% at 20 min; and 90 (7)% vs 53 (33)% at 30 min). WTF had returned to baseline after 48 h of reperfusion in the presence or absence of naloxone.

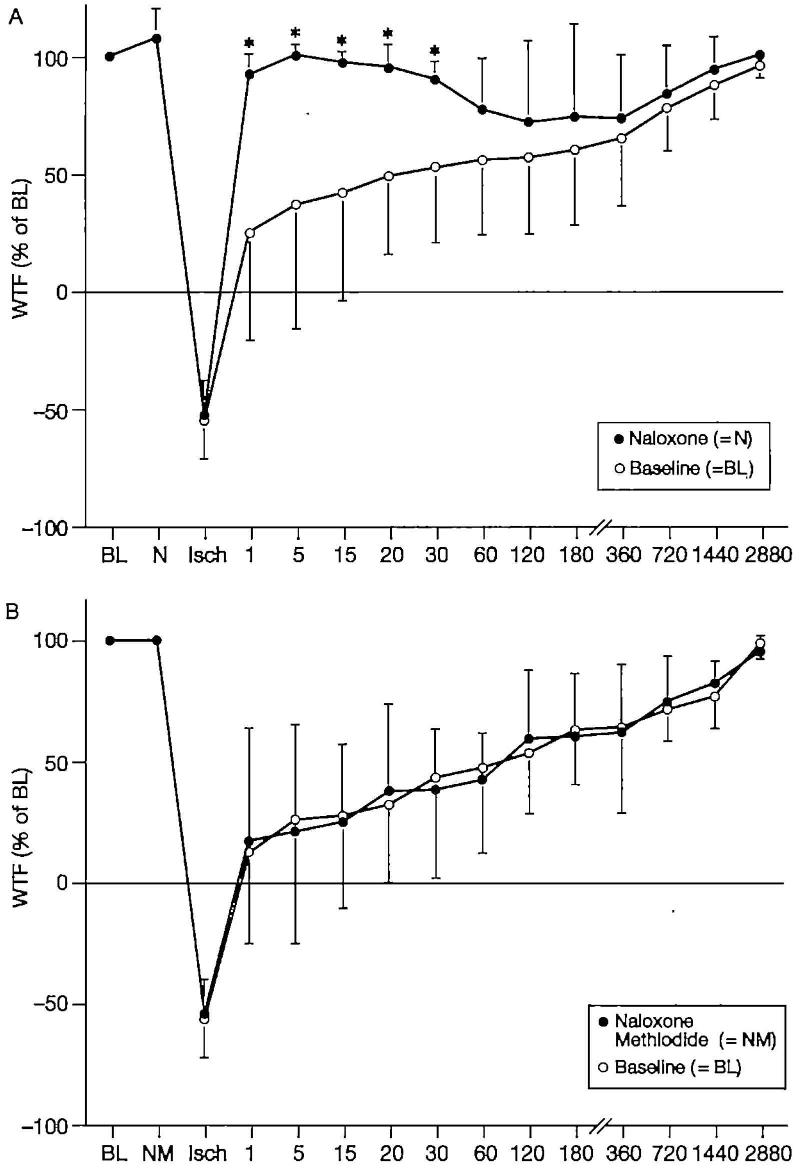

Fig 1 Wall-thickening fraction (WTF) of the area perfused by the left anterior descending coronary artery as a percentage of control values during the reperfusion period for naloxone (A) and naloxone methiodide (B). Data are presented as mean±SD and *P* values refer to between-group differences. BL=baseline values. N=naloxone. NS=not significant. Isch=ischaemia (10 min). *$P<0.05$.

Regional myocardial blood flow

During LAD occlusion, subendocardial blood flow decreased significantly, from 0.71 (0.22) to 0.09 (0.01) ml g^{-1} min^{-1} in the absence of naloxone, from 1.03 (0.25) to 0.11 (0.03) ml g^{-1} min^{-1} in the presence of naloxone ($P<0.05$), from 0.69 (0.16) to 0.07 (0.01) ml g^{-1} min^{-1} in the absence of naloxone methiodide, and from 0.72 (0.28) to 0.10 (0.01) ml g^{-1} min^{-1} in the presence of naloxone methiodide. Only administration of naloxone, and not administration of naloxone methiodide, in the absence of ischaemia significantly increased subendocardial blood flow of the LAD-perfused areas (0.71 (0.22) vs 1.03 (0.25) ml g^{-1} min^{-1}). Without ischaemia, only naloxone significantly increased blood flow ratio between the subendocardial and the subepicardial layers (endocardial/epicardial) in the LAD-perfused area (1.13 (0.66) vs 2.06 (1.17) ml g^{-1} min^{-1}). The blood flow ratio to the subendocardial layers between the occluded zone (LAD-perfused area) (occluded/normal) during ischaemia was not different with and without naloxone, or with and without naloxone methiodide.

Discussion

In this model, naloxone improved the functional recovery from myocardial stunning and improved ischaemic and postischaemic systolic left ventricular performance. Dose–response studies of naloxone in dogs are not available, but naloxone has been used for several scientific purposes in dogs. The dose used in our study (63 μg kg^{-1})

antagonizes the μ-agonist effects in dogs.[8] EOPs are found in central areas near the cardiovascular centers of the brain, in the hypothalamus, and peripherally in the myocardium.[10] Naloxone exerts central and peripheral effects on heart tissue itself.[11] However, the above-described protective effects of naloxone are probably mainly mediated by antagonistic action against central opioid receptors.[2] The opioid receptor antagonist naloxone methylbromide, which unlike naloxone does not cross the blood–brain barrier, did not produce an increase in regional blood flows in dogs with right-sided congestive heart failure.[12] These data are in agreement with our findings. Central effects of naloxone are therefore predominant and probably occur mainly in the hypothalamus.[13] The central sites at which naloxone exerts this action have not been determined. EOPs, released upon myocardial ischaemia,[1] activate central opioid receptors, leading to sympathoinhibition and contributing to negative inotropic effects on the myocardium. Experimental data suggest that the increased endogenous opioids during heart failure act mainly at δ-receptors[14] and κ-receptors.[15] Activation of these receptors decreases myocardial mechanical performance and alters regional blood flow distribution. It has been suggested that the effects of sigma receptor ligands are mediated via two receptor subtypes, of which one has positive and the other negative inotropic activity.[16] It is not clear which effect is predominant. Pharmacological studies led to the proposal that myocardial ε-opioid receptors do not play an important role, at least in cardiac rhythm.[17] In contrast, antiarrhythmic effects mediated by δ-,[18] μ-, κ-receptor agonists and σ-receptor-mediated proarrhythmic effects have been described.[17] Interestingly, μ-receptors are only expressed at early periods in heart ontogeny. Also, there is a period in which the density of μ- (but not κ- and δ-) receptors decreases dramatically.[19] This might explain, at least in part, the dose-related variability and species differences of opioid receptor-mediated effects.[20] Selective opioid receptor blockade might provide a starting point for effective treatment of the negative inotropic effects of myocardial stunning. However, further investigations in this area will be needed.

It should be borne in mind that the results obtained here are restricted to dogs; there may be species differences in the severity and duration of the ischaemic response and its modulation by naloxone. Also, the lack of a dose–response precludes extrapolation of the data to other doses of naloxone.

In conclusion, naloxone improves ischaemic and post-ischaemic systolic impairment and reduces the severity of myocardial stunning in chronically instrumented dogs. This study is the first to suggest that central opioid receptors are involved in recovery from myocardial stunning.

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Effects of sevoflurane on dopamine, glutamate and aspartate release in an *in vitro* model of cerebral ischaemia

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Release of excitatory amino acids and dopamine plays a central role in neuronal damage after cerebral ischaemia. In the present study, we used an *in vitro* model of ischaemia to investigate the effects of sevoflurane on dopamine, glutamate and aspartate efflux from rat corticostriatal slices. Slices were superfused with artificial cerebrospinal fluid at 34°C and episodes of 'ischaemia' were mimicked by removal of oxygen and reduction in glucose concentration from 4 to 2 mmol litre^{-1} for $\leqslant$30 min. Dopamine efflux was monitored *in situ* by voltammetry while glutamate and aspartate concentrations in samples of the superfusate were measured by HPLC with fluorescence detection. Neurotransmitter outflow from slices was measured in the absence or presence of sevoflurane (4%). After induction of ischaemia in control slices, there was a mean (SEM) delay of 166 (7) s (n=5) before sudden efflux of dopamine which reached a maximum extracellular concentration of 77.0 (15.2) µmol litre^{-1}. Sevoflurane (4%) reduced the rate of dopamine efflux during ischaemia (6.90 (1.5) and 4.73 (1.76) µmol litre^{-1} s^{-1} in controls and sevoflurane-treated slices, respectively; P<0.05), without affecting its onset or magnitude. Excitatory amino acid efflux was much slower. Ischaemia-induced glutamate efflux had not reached maximum after 30 min of ischaemia. Basal (pre-ischaemic) glutamate and aspartate efflux per slice was 94.8 (24.8) and 69.3 (31.5) nmol litre^{-1} superfusate (n=4) and was not significantly reduced by 4% sevoflurane. Ischaemia greatly increased glutamate and aspartate efflux (to a maximum of 919 (244)% and 974 (489)% of control, respectively). However, ischaemia-induced efflux of both glutamate and aspartate was significantly reduced by 4% sevoflurane (P<0.001 for glutamate, P<0.01 for aspartate). In summary, sevoflurane may owe part of its reported neuroprotective effect to a reduction of ischaemia-induced efflux of excitatory amino acids and, to a lesser extent, dopamine.

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Sevoflurane is a volatile anaesthetic suitable for both induction and maintenance of anaesthesia.[1] Clinically, it produces a pattern of rapid recovery with little excitation on emergence.[2] Its capacity to increase cerebral blood flow[3] whilst preserving cerebral autoregulation[4] makes it an attractive agent for the preservation of neuronal function.

There is some evidence from animal studies that sevoflurane is neuroprotective in models of cerebral ischaemia.[5] Since global ischaemic insults, and even frank infarcts, can occur in a theatre setting, a neuroprotective anaesthetic is of considerable clinical interest.

During cerebral ischaemia, a cascade of events occur that result in neuronal death. One of the earliest of these is the release of neurotransmitters, in particular the excitatory amino acids.[6] Reduction of transmitter release thus represents a possible mechanism by which drugs may exert a neuroprotective effect.

Previous work in this laboratory has examined transmitter efflux in an *in vitro* model of cerebral ischaemia based on brain slices.[7] We have found that various recognized neuroprotective agents reduce neurotransmitter efflux. In particular, we recently found that halothane slowed

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ischaemia-induced dopamine efflux.[8] In the present study we examined the effects of sevoflurane on the efflux of dopamine, glutamate and aspartate.

Materials and methods

Preparation of brain slices

Male Wistar rats (150–300 g) were killed by cervical dislocation. No prior neuroprotective agents were administered. The cranial vault was opened and the brain excised while irrigated with ice-cold (–1 to +1°C) oxygenated artificial cerebrospinal fluid (aCSF) throughout. Coronal corticostriatal slices (350 μm thick: –0.7 to +1.3 mm *vs* bregma[9]) were prepared using a Campden 752M vibratome and transferred to a 'slice saver' containing 500 ml continuously oxygenated (95% oxygen/5% carbon dioxide) aCSF maintained at room temperature (24°C) where they were incubated for 1–4 h to allow recovery from the trauma induced by preparation.

Standard aCSF (pH 7.4) was used, consisting of (mmol litre^{-1}) NaCl (126.0), KCl (4.0), KH_2PO_4 (1.4), $MgSO_4$ (1.3), $CaCl_2$ (2.4), $NaHCO_3$ (26.0), (+)-glucose (4.0) and ascorbic acid (0.4). The glucose concentration was reduced to 2 mmol litre^{-1} during the induction of ischaemia.

Induction of 'ischaemia'

After recovery in the saver, the slices were transferred to a submersion-type recording chamber, modified as previously described[7], and superfused with aCSF for 30 min before induction of ischaemia. For the measurement of dopamine, single slices were placed in the chamber and perfused with aCSF at 400 ml h^{-1}. For excitatory amino acid experiments, four slices were carefully chosen so as to allow comparison between sets of slices. In these experiments, slices were used within 90 min of cutting and four slices were then superfused together in a single chamber at 300 ml h^{-1}, in order to enhance the detection of glutamate and aspartate efflux.

The superfusion system comprised separate flasks of 'maintenance' or 'ischaemic' aCSF, gassed with 95% oxygen/5% carbon dioxide or 95% nitrogen/5% carbon dioxide, respectively, and pumped into the slice chamber by a Watson-Marlow 302M peristaltic pump via gas-impermeable (Marprene) tubing. The temperature of the slice chamber was maintained at 34.0 (0.2)°C throughout. After 30 min of superfusion with maintenance aCSF, superfusion with 'ischaemic' aCSF was initiated for 30 min.

Sevoflurane was applied to the brain slices at 4% (approximately 1.7 MAC[10]) throughout the experiment (during both pre-incubation in maintenance aCSF and imposition of ischaemia) via a calibrated Blease Datum vaporizer.

Detection of dopamine efflux

Ischaemia-induced dopamine efflux was measured using fast cyclic voltammetry.[7] Carbon fibre microelectrodes, 7 μm in diameter, were positioned in the dorsolateral zone of the striatum, under micromanipulator control. Auxiliary (stainless steel) and reference (Ag/AgCl) electrodes were located at convenient points in the slice chamber where they would not obstruct the voltammetric or d.c. potential electrodes. Voltammetric scans (–1.0 to +1.4 V compared with reference electrodes, 480 V s^{-1}) were performed every 4 s with a Millar Voltammetric Analyser (PD Systems, West Molesey, UK). A 'sample-and-hold' record of current at the peak dopamine oxidation voltage (+0.6 V compared with reference electrodes) was displayed on a chart recorder while entire voltammetric scans were recorded on a digital storage oscilloscope (Nicolet 310 Series) and saved on to floppy disk. At the end of the experiment, the carbon fibre microelectrodes were calibrated by standard flow injection analysis (400 ml h^{-1}) in solutions of dopamine (500 μl of 100 μmol litre^{-1}).

Three dopamine efflux variables were measured: the time from initiation of ischaemia to the onset of dopamine efflux (t_{on}, in s), the maximum extracellular dopamine concentration (DA_{max}, in μmol litre^{-1}) and the mean rate of dopamine efflux from t_{on} to DA_{max} ($\delta DA/\delta t$, in μmol litre^{-1} s^{-1}).

Detection of excitatory amino acid efflux

At 5 min intervals throughout the experiment, a 1 min sample (5 ml) of slice superfusate was collected into glass vials and frozen until analysed for glutamate and aspartate content. Glutamate and aspartate were determined using a modification of the HPLC method of Smolders and colleagues.[11] The method is based on the derivatization of amino acids using *o*-phthaldialdehyde (OPA). A stock solution of 120 mg OPA in 6 ml methanol was prepared. Derivatizing reagent was prepared by mixing 0.6 ml OPA solution with 5.4 ml borate buffer (pH 9.0) and 60 μl 2-mercaptoethanol. Equal volumes (50 μl) of superfusates collected from slices and derivatizing reagent were mixed at room temperature (24–26°C) and, exactly 2 min later, 50 μl were injected into the chromatograph.

The OPA derivatives were separated on a 100×3.2 mm i.d. HIRPB column (HiChrom, Reading, UK) eluted with 10% HPLC-grade acetonitrile in 0.1 M sodium acetate buffer (pH 6.0) at 1 ml min^{-1} with an Altex 110 pump (Beckman, High Wycombe, UK). The compounds were detected on a Perkin–Elmer LS-4 fluorimeter (Beaconsfield, UK) with the excitation monochromator set at 350 nm and the emission set at 450 nm. Peaks were recorded on an analogue recorder or digitally using a 16 bit A/D converter (Jones Chromatography, Hengoed, UK) in an ICL M55 computer. Four minutes after the injection, the column was washed with 90% acetonitrile in water for 1 min, using a second Altex pump and an electronic valve actuator (Jones Chromatography) controlled from the computer. The column was equilibrated with eluent for 5 min before the next injection. Calibration curves were generated using standard solutions in water containing 125–1000 nmol litre^{-1}

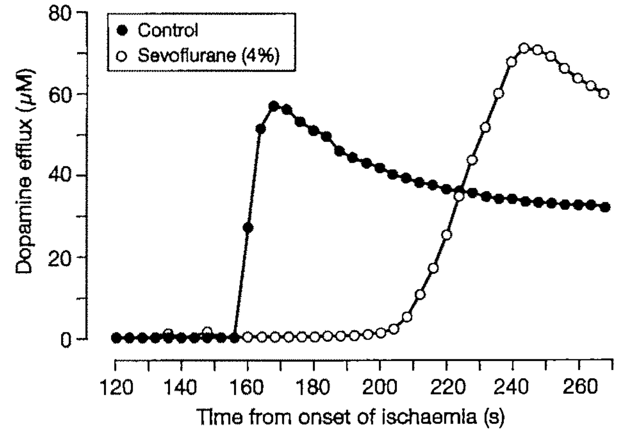

Fig 1 Effect of 4% sevoflurane (open circles) on ischaemia-evoked dopamine efflux from rat striatal slices. Controls (filled circles) are shown for comparison. Data from a single representative experiment. Note that the abcissa begins at 120 s and is expanded to emphasize differences in $\delta DA/\delta t$.

glutamate and aspartate and data were expressed as nmol of amino acid litre^{-1} superfusate per slice.

For estimation of variability, calibration solutions were prepared in the range 1–0.031 μmol litre^{-1}, plus blank. Estimates of the intra- and inter-assay precision and accuracy values were obtained by quintuplicate analyses of solutions containing 1, 0.5, 0.2, 0.1, 0.05 and 0.02 μmol litre^{-1} of aspartate and glutamate. Intra-assay coefficients of variation of replicate analyses of glutamate and aspartate concentrations were between 2 and 6%. The lower limit of quantification was taken as 0.05 μmol litre^{-1} as coefficients of variation for samples at 0.02 μmol litre^{-1} were >20%.

Drugs and chemicals

All chemicals used to make the aCSF were of standard AnalaR grade from BDH Lab supplies (Poole, UK). Dopamine was obtained from Sigma (Poole, UK). Sevoflurane was a gift from Abbott Laboratories Ltd.

Data analysis

The effects of sevoflurane on ischaemia-induced excitatory amino acid efflux were calculated as percentages of pre-ischaemia values and were compared with control by two-way analysis of variance (ANOVA). The effects of sevoflurane on basal (pre-ischaemic) glutamate and aspartate efflux were analysed by unpaired *t*-tests. The effects of sevoflurane on individual measures of dopamine efflux were tested using paired *t*-tests.

Results

Induction of a period of ischaemia (hypoxia/hypoglycaemia) in slices at 34°C resulted in a consistent pattern of striatal dopamine efflux in untreated control tissue. After an initial period of quiescence lasting 2–3 min, there was a sudden efflux of dopamine, typically reaching a peak extracellular concentration of 50–100 μmol litre^{-1} within 20 s before falling slowly back towards baseline over a period of several minutes. Figure 1 shows a representative profile of dopamine efflux in control and sevoflurane-treated striatal slices.

Table 1 Basal excitatory amino acid efflux from corticostriatal slices. Mean (SEM), n=4 (controls), n=5 (sevoflurane)

Amino acid	Basal amino acid efflux per slice (nmol litre^{-1} superfusate)	
	Controls	4% Sevoflurane
Aspartate	69.3 (31.5)	42.5 (12.8)
Glutamate	94.8 (24.8)	66.5 (18.3)

Although the onset of dopamine efflux appeared longer in 4% sevoflurane (mean (SEM) t_{on} 166 (7) s in controls, 211 (64) s in sevoflurane-treated slices; n=5), this was not significant (note the truncated x-axis in Figure 1). Sevoflurane did not significantly reduce the maximum level of dopamine efflux (DA_{max} 77.0 (15.2) and 67.8 (12.4) μmol litre^{-1} in controls and sevoflurane-treated slices, respectively). However, the rate of dopamine efflux was significantly lower in slices exposed to sevoflurane ($\delta DA/\delta t$ 6.90 (1.5) and 4.73 (1.76) μmol litre^{-1} s^{-1} in controls and sevoflurane-treated slices, respectively; $P<0.01$).

Basal excitatory amino acid efflux in the superfusate was not significantly different in control slices and those treated with 4% sevoflurane (Table 1). The effects of ischaemia on excitatory amino acid efflux were very different from those on dopamine efflux. Figure 2 shows the effect of sevoflurane on ischaemia-induced glutamate efflux. After imposition of ischaemia, there was a significant ($P<0.001$) time-dependent increase in glutamate efflux over the 30 min course of the ischaemic episode. This was significantly reduced in the presence of 4% sevoflurane ($P<0.001$; two-way ANOVA).

A similar profile was observed with aspartate. The effect of sevoflurane on ischaemia-induced aspartate efflux is shown in Figure 3. As with glutamate, there was a substantial increase in aspartate efflux over the duration of the ischaemic episode. This was essentially abolished in the presence of 4% sevoflurane ($P<0.01$; two-way ANOVA).

Discussion

The role of excitatory amino acids in ischaemic damage is well established. Efflux of glutamate and/or aspartate is an early event in a cascade that leads to neuronal death and drugs that block the postsynaptic actions of excitatory amino acids at *N*-methyl-D-aspartate (NMDA) or alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors have been shown to be neuroprotective in

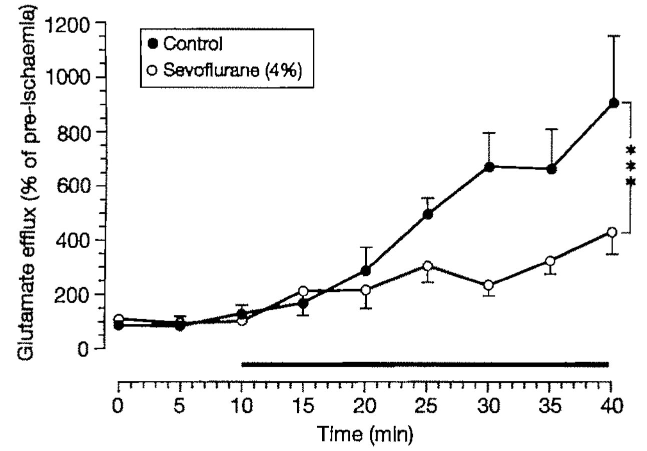

Fig 2 Effect of 4% sevoflurane (open circles) on ischaemia-evoked glutamate efflux from corticostriatal slices (expressed as a percentage of pre-ischaemic values). All values are means ± SEM (n=4 or 5). Controls (filled circles) are shown for comparison. $^{***}P<0.001$ (two-way ANOVA). The period of ischaemia is indicated by the horizontal bar.

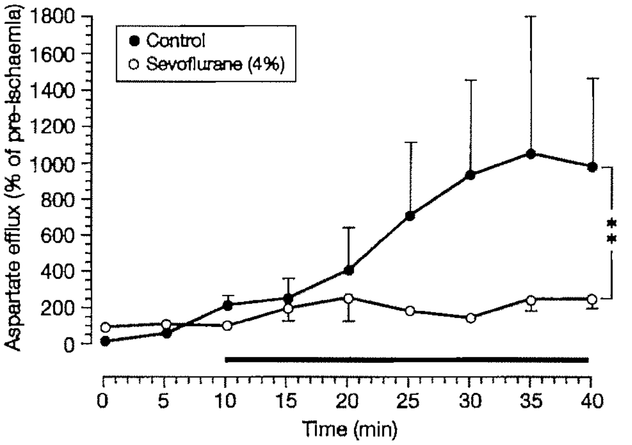

Fig 3 Effect of 4% sevoflurane (open circles) on ischaemia-evoked aspartate efflux from corticostriatal slices (expressed as a percentage of pre-ischaemic values). All values are means ± SEM (n=4 or 5). Controls (filled circles) are shown for comparison. $^{**}P<0.01$ (two-way ANOVA). The period of ischaemia is indicated by the horizontal bar.

ischaemia.[12] However, glutamate is only one of many transmitters released in ischaemia. Recent reports have suggested that dopamine released in ischaemia may also mediate neuronal damage, at least in the striatum and at least partly through an interaction with D_2 receptors.[13]

An alternative approach to neuroprotection, rather than blocking postsynaptic actions, is to prevent the efflux of neurotransmitter. Studies by our group have shown that ischaemia-induced dopamine efflux may be attenuated or delayed by several agents or strategies with neuroprotective potential. These include blockers of calcium and sodium channels,[14,15] NMDA antagonists[16] and hypothermia.[17]

Efflux of glutamate and aspartate in ischaemia is sometimes held to be mediated by reversal of the glutamate carrier.[18] The mechanism of dopamine efflux is less clear. Whilst at least one group has suggested that it too occurs through reversal of the transporter,[19] we found no effect of dopamine uptake inhibitors on ischaemia-induced dopamine efflux and thus suggested that its primary mode of release was exocytotic.[7]

The possibility that general anaesthetics are neuroprotective is widely promoted.[20] Although ketamine is known to be neuroprotective, presumably because of its capacity to block NMDA receptors, it is possible that others with less overt actions may also be protective. We have recently shown that halothane is able to slow dopamine efflux in this model.[8]

In the present study, we found that sevoflurane not only slowed ischaemia-induced dopamine efflux in a manner similar to halothane but also reduced release of glutamate and aspartate. The effect on aspartate was particularly striking. However, since aspartate binds to NMDA receptors with approximately a tenth of the affinity of glutamate,[21] such a large reduction in its release is likely to have less neuroprotective consequences than the diminution of glutamate release.

It should be said that in measuring dopamine efflux by voltammetry, we have examined the effect of sevoflurane on ischaemia-induced transmitter release from striatal terminals, whereas with the method for investigating excitatory amino acid efflux, we have examined transmitter release from cells and synaptic terminals in both the cortex and striatum. It would be interesting to discover if the differential effect of sevoflurane on maximal ischaemia-induced transmitter release lies in this different neuroanatomical source of transmitter or whether it reflects true differences in the mode of action of the anaesthetic on the different transmitter systems *per se*. Such questions might be resolved by electrode-based techniques, but these have not yet reached the technological level required for such studies.

Sevoflurane has been reported to be an effective neuroprotective agent in cerebral ischaemia. For instance, Werner and colleagues[22] found that sevoflurane improved outcome after a focal ischaemic insult in rats. Sevoflurane also expedites the recovery of brain energy metabolism, relative to halothane, in global ischaemia.[23]

In common with other volatile anaesthetics, sevoflurane has many biochemical actions. It blocks nicotinic receptors[24] whilst enhancing the effects of agonist stimulation at γ-amino-butyrate $(GABA)_A$ and $GABA_B$ receptors.[25] Recently, Li and Pearce[26] showed that halothane enhanced the effects of GABA at $GABA_A$ receptors by slowing the dissociation of the agonist; they suggested that this may be a major mode of action of other volatile anaesthetic agents. Also of interest in the context of the present report, a recent study found that sevoflurane enhanced glutamate uptake by astrocytes.[27] Such an effect could contribute to the decreased efflux not only of glutamate observed here but also of aspartate, which is also a substrate for the transporter.[28]

The volatile anaesthetics have also been shown to activate potassium channels whilst blocking sodium channels in rat brain slice preparations.[29] We have previously shown that sodium channel blockade slows ischaemia-induced dopamine efflux in striatal slices,[15] so it is possible that such a mechanism underlies some of the effects of sevoflurane observed here.

Throughout this study, sevoflurane administration was initiated before the ischaemic insult. Although this has little bearing on the treatment of stroke, where neuroprotection can only be administered in a post-ictal manner, such a circumstance would be analogous to that found in the operating theatre, where an ischaemic episode might occur under anaesthesia. Surgery for carotid endarterectomy or coronary artery bypass grafting carries a significant risk of cerebral ischaemia, so there is a role for prior administration of appropriate neuroprotectants. The results of the present study show that sevoflurane, at a clinically relevant concentration (approximately 1.7 MAC[10]), can reduce the efflux of neurotoxic transmitters under such conditions and thus may be neuroprotective.

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REVIEW ARTICLE

Neurofibromatosis: clinical presentations and anaesthetic implications

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The neurofibromatoses are autosomal dominant diseases that have widespread effects on ectodermal and mesodermal tissue. The commonest member of the group is neurofibromatosis type I (NFI) which varies in severity but which can affect all physiological systems. Neurofibromas are the characteristic lesions of the condition and not only occur in the neuraxis but may also be found in the oropharynx and larynx; these may produce difficulties with laryngoscopy and tracheal intubation. Pulmonary pathology includes pulmonary fibrosis and cystic lung disease. The cardiovascular manifestations of NFI include hypertension, which may be associated with phaeochromocytoma or renal artery stenosis. Neurofibromas may also affect the gastrointestinal tract and carcinoid tumours may be found in the duodenum. This review documents the aetiology and clinical manifestations of the neurofibromatoses and discusses their relevance to the anaesthetist.

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Keywords: complications, neurofibromatosis; anaesthesia

The neurofibromatoses are a group of hereditary diseases transmitted in an autosomal dominant fashion and are characterized by a tendency to formation of tumours of ectodermal and mesodermal tissues. They represent the most common example of the neurocutaneous syndromes, a group that also includes tuberous sclerosis, von Hippel-Lindau disease and the basal nevus syndrome.[52]

Although the neurofibromatoses have common characteristics, two distinct forms have been recognized on clinical and genetic grounds. These are designated neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2).

Neurofibromatosis type 1 (von Recklinghausen's neurofibromatosis, peripheral neurofibromatosis)

Reports detailing probable cases of neurofibromatosis have appeared since the 16th century.[3] The first review of the disease was published in 1849 by the Dublin Professor of Surgery, Robert W. Smith,[94] who suggested that the origin of the tumours was the connective tissue surrounding small nerves.[34] It was Freidrich von Recklinghausen in 1882 who first recognized that the tumours that characterize the disease arise from nervous tissue;[106] his name has since been inextricably linked with the condition.

Genetics and pathophysiology of NF1

The birth incidence of NF1 lies between 1 in 2500–3300 and its prevalence in the population is 1 in 5000;[13] it is inherited in an autosomal dominant manner. Although the condition shows almost 100% penetrance, it has a variable expressivity (i.e. there may be considerable variation of clinical manifestations within a family). In addition, in 30–50% of cases there is no family history; these 'sporadic' cases probably arise from (usually paternal) germ cell mutations.[68]

Using genetic linkage studies, the gene for NF1 has been localized to chromosome 17q 11.2. The gene spans over 350 kb of genomic DNA and encodes a protein containing 2818 amino acids.[55] This protein has been named neurofibromin and appears to have a tumour suppressive role. Mutations at the NF1 gene result in diminished levels of neurofibromin with resultant development of the wide variety of tumours seen in the disease.[105]

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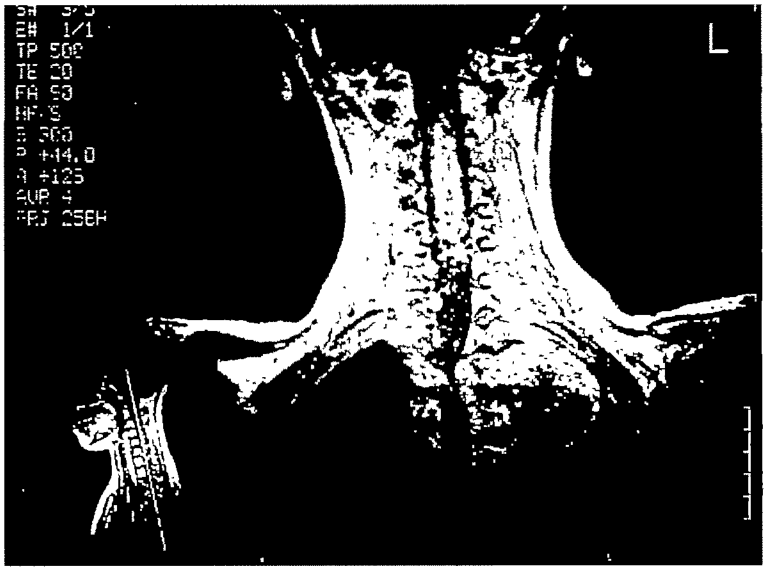

Fig 1 Coronal T_1 weighted MRI showing large dumbbell neurofibroma in T_2/T_3 intervertebral foramen and occupying the apex of the left thoracic cavity and displacing the spinal cord to the right.

Diagnostic features of NF1

Despite major advances in the molecular genetics of NF1, diagnosis remains largely based on clinical criteria (Table 1).[35]

Café-au-lait spots are symmetrical flat areas of skin hyperpigmentation with rounded edges and are seen in newborns with NF1; their number and size increase during infancy. By adulthood, about 95% of NF1 patients have café-au-lait spots. Their presence suggests NF1 although familial cafe-au-lait spots do occur rarely. In addition, 70% show freckling of the intertriginous area of the axilla or groin.[45]

Neurofibromas are the major feature of NF1 and fall into three clinically and histologically distinct types.[109] *Cutaneous* neurofibromas occur in more than 95% of patients, and are discrete, benign tumours found within the dermis. *Nodular* neurofibromas arise in peripheral nerves and may be found at any site; despite their size, they do not infiltrate surrounding tissues. Paraspinal neurofibromas may grow to an enormous size, giving rise to the classic thoracic 'dumbbell' tumour (Fig. 1).

Plexiform neurofibromas are the hallmark lesion of NF1. These occur in 30% of NF1 patients, are usually congenital, and affect long portions of the nerve involved; infiltration of the nerve itself and the surrounding tissue may occur, giving rise to extensive disfiguration. It is thought that John Merrick, the Elephant Man, may have suffered from plexiform neurofibromatosis[108] although proteus now appears to be a more likely diagnosis.[100] Apart from the obvious mechanical complications of such tumours, plexiform neurofibromas have a tendency, albeit rare, to undergo malignant change forming *malignant peripheral nerve sheath tumours*. Malignant progression occurs in 2–16% of patients and is the major cause of morbidity and mortality in NF1.[51]

Table 1 Diagnostic criteria for NF1

The patient should have two or more of the following:

1. Six or more café-au-lait spots
   1.5 cm or larger in post-pubertal individuals
   0.5 cm or larger in pre-pubertal individuals
2. Two or more neurofibromas of any type or one or more plexiform neurofibroma
3. Axillary or groin freckling
4. Optic glioma
5. Two or more Lisch nodules (benign melanotic iris hamartomas)
6. A distinctive bony lesion
   Dysplasia of the sphenoid bone
   Dysplasia or thinning of long bone cortex
7. A first degree relative with NF1

Pilocytic astrocytomas are a benign form of astrocytoma, and when arising from the optic nerve or chiasm, are termed optic gliomas. They are seen in 15% of NF1 patients on MRI and are symptomatic in 2–5%; they are slow growing and generally do not undergo malignant change.[57]

About 95% of individuals with NF1 will develop Lisch nodules—benign multiple melanotic hamartomas of the iris.[46] Finally, distinctive bony lesions including dysplasia of the sphenoid wing and thinning of long bones contribute to the diagnostic criteria of NF1.[28]

Other tumours found in NF1

In addition to the neurofibromas that characterize the disease, other tumours occur more commonly in NF1. Phaeochromocytoma occurs more commonly in NF1 patients than in the general population.[58] Although the features of some of the multiple endocrine neoplasia

Table 2 Diagnostic criteria for NF2

The following features confirm NF2:
Bilateral vestibular schwannomas (VS)
Or
Family history of NF2 (first degree relative) *plus:*
1. Unilateral vestibular schwannoma in patient <30 yr old; or
2. Any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

The following features indicate probable NF2:
Unilateral vestibular schwannoma in patient <30 yr old plus at least one of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
Multiple meningiomas (two or more) plus unilateral vestibular schwannoma in patient <30 yr old or one of the following: glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

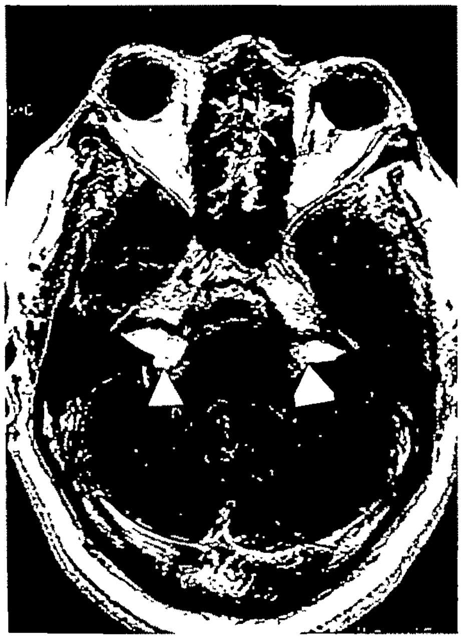

Fig 2 Contrast enhanced T_1 weighted image showing bilateral intracanalicular vestibular schwannomas (arrows) projecting into the cerebellopontine angles.

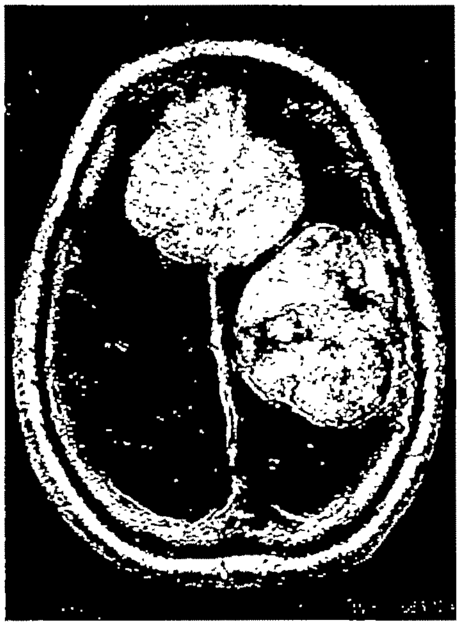

Fig 3 Frontal falx meningioma extending bilaterally and left frontoparietal convexity meningioma in same patient as Figure 2.

syndromes overlap with NF1 (e.g. neural crest origin tumours), no association between the two conditions has been established.[41] Intestinal tumours are commonly seen in NF1 patients and interestingly have a predilection for the duodenum and especially the ampulla of Vater.[50] Malignant gliomas are found in approximately 2% of patients with NF1.[102] Finally, the association of juvenile chronic myeloid leukaemia with NF1 has helped in the identification of the role of the NF1 gene as a tumour suppressive gene.[7]

Additional features of NF1

Patients with NF1 often demonstrate relative macrocephaly and tend to be, on average, shorter in stature. Pituitary abnormalities include growth hormone deficiency and central precocious puberty which may occur in the absence of optic chiasm gliomas;[12] radiotherapy treatment of the latter may increase the risk of growth retardation and intellectual deficits.[1] Learning disabilities occur in 50% of patients. However, the relationship between lower range IQ and the presence of so called ‘unidentified bright objects’ seen in the basal ganglia, thalamus and brainstem on T_2 weighted MRI imaging in 70% of patients remains controversial.[73] Mental retardation (full scale IQ less than 70) is only slightly more frequent than that of the general population. While some social handicap might be expected in severely affected sufferers, no uniform psychiatric syndrome is encountered.[67]

Other conditions which occur more commonly in the NF1 population include epilepsy,[53] headaches,[80] aqueduct stenosis[90] and hydrocephalus. Although the incidence of vestibular schwannoma is probably no greater than that of the general population, deafness is common.[16] Delayed central conduction times of auditory brain stem evoked potentials have been observed[76] and conductive hearing loss may be the consequence of bony deformity or tumour within the auditory meatus.[60]

Table 3 Anaesthetic considerations of NF1

System	Comments
Airway	Neurofibroma of tongue, pharnyx or larynx may interfere with tracheal intubation Suspicion raised by history of dysphagia, dysarthria, stridor or change of voice
Respiratory system	Intrapulmonary neurofibroma, pulmonary fibrosis may produce cough and dyspnoea Right ventricular failure may be present Scoliosis/kyphosis may compromise lung function
Cardiovascular system	Raised arterial pressure usually essential hypertension but consider phaeochromocytoma or renal artery stenosis Hypertrophic cardiomyopathy may occur Mediastinal tumours may result in superior vena caval obstruction
Central nervous system	Cerebral and spinal neurofibromas common Increased incidence of epilepsy and learning disorders Cerebrovascular disease may co-exist
Gastrointestinal tract	Intestinal tumours may present with pain, gastrointestinal haemorrhage or perforation Carcinoid tumours occur in duodenum and may result in jaundice and carcinoid syndrome
Genitourinary system	Neurofibromas may cause ureteric/urethral obstruction
Musculoskeletal system	Vertebral deformities or spinal cord tumours may make spinal/extradural techniques difficult

Neurofibromatosis type 2 (bilateral acoustic neurofibromatosis, central neurofibromatosis)

The recognition of a group of patients with familial tendency to pass on bilateral acoustic neuromas (vestibular schwannomas) coupled with genetic studies has resulted in the recognition of NF2 as a distinct entity;[49] this division in the neurofibromatoses is important both in the management and genetic counselling of patients.

Genetics and pathophysiology of NF2

The birth incidence of NF2 lies between 1 in 33 000–40 000 with a prevalence within the population of 1 in 210 000.[44] It is inherited in an autosomal dominant fashion; however, in common with NF1, 50% of cases represent sporadic gene mutations.[27] Using genetic analysis of large pedigrees, the NF2 gene has been shown to reside on chromosome 22q 12.1 and the gene has recently been cloned. It spans 110 kb of genomic DNA and encodes a cytoskeletal protein known as merlin or schwannomin.[20] It appears that the NF2 gene acts as a tumour suppressor, both in NF2, sporadic meningiomatosis and other neuroectodermal tumours.[19] Although there appears to be some correlation between genotype and phenotype, there are exceptions. Limited gene analysis is now available and may be useful for genetic counselling.

Diagnostic features of NF2

As with NF1, diagnosis depends largely on the recognition of clinical features (Table 2).[35]

The defining feature of NF2 is the presence of bilateral vestibular schwannomas—tumours arising from the vestibular branch of the VIII cranial nerve (Fig. 2).

Patients typically present with a gradual, progressive and often asymmetrical hearing loss although sudden hearing loss may occur. The mean age of onset of symptoms is 24 yr whilst non-NF patients with sporadic tumours present in their mid-forties.[26] Whilst the occurrence of bilateral vestibular schwannomas confirms NF2, the presence of a unilateral vestibular schwannoma in conjunction with other NF2 associated features should raise the possibility of NF2.

These features result from abnormal growth in certain cell types and include meningiomas (Fig. 3), other schwannomas, gliomas and juvenile posterior subcapsular lenticular opacities and cortical cataracts. Although neurofibromas can occur, plexiform morphology is not seen in NF2. A non-specific finding in NF2 is intracerebral calcification.

Segmental neurofibromatosis

Both NF1 and NF2 can present as a non-generalized form in which only one body part is affected. This so-called 'segmental neurofibromatosis' appears to represent somatic mosaicism in which only some cells possess the NF1 or NF2 gene mutation. Depending on the segment affected, the risk to offspring may be very much lower than the 50% risk for generalized disease. Other 'incomplete' forms of neurofibromatosis may involve balanced translocations, and may be familial with dominant inheritance patterns. A wide variety of clinical pictures has therefore been described and classified.

Anaesthetic considerations of neurofibromatosis

Because of the relative rarity and the only relatively recent recognition of NF2 as a distinct entity, most of the literature concerning the medical and anaesthetic complications of neurofibromatosis relates to NF1. As the neurofibromatoses affect both ectodermal and mesodermal tissue, it is unsurprising that all systems of the body may be involved (Table 3).

Airway

An estimated 5% of patients with NF1 have an intra-oral manifestation of the disease.[5] Discrete neurofibromas may involve the tongue[93 94] or the larynx.[10 30] When the latter is involved it is often the aryepiglottic fold or arytenoids that are affected, presumably reflecting those areas most rich in terminal nerve plexuses.[47] Unilateral vocal cord palsy has been reported secondary to involvement of the recurrent laryngeal nerve.[79] Discrete and plexiform neurofibromas commonly occur in the cervical region and large tumours of the parapharyngeal space may result in distortion of the airway. Pathologies in NF1 that affect the tongue, larynx and cervical tissues may cause obstruction, and symptoms of dyspnoea, stridor, loss or change of voice or dysphagia should warn the anaesthetist of potential airway problems. Suspicion warrants specialist examination with indirect laryngoscopy and CT or MR imaging.

Airway obstruction after induction of anaesthesia has been reported in patients with a tongue neurofibroma[14] and a neurofibroma involving the laryngeal inlet.[78] Both patients required emergency tracheostomy. Even if intra-oral pathology is recognized pre-operatively, elective awake fibreoptic tracheal intubation may fail because of a grossly distorted anatomy.[113] However, successful intubation after inhalation anaesthesia with sevoflurane has been described.[107]

In addition, the presence of macroglossia, macrocephaly, specific mandibular abnormalities[54] and cervical spine involvement may contribute to difficulties of airway management. Painless dislocation of cervical vertebrae has been reported in a patient with multiple cervical neurofibroma and it has been suggested that radiographic examination of the neck should be performed before anaesthesia in these patients in order to avoid spinal cord damage during laryngoscopy and tracheal intubation.[59]

Respiratory system

Neurofibromatosis may affect the conducting airways, lung parenchyma, the thoracic cage and the chest wall.

Conducting airways

Mediastinal neurofibromas usually originate in the posterior mediastinum or spread from the retroperitoneal space or cervical paraspinal areas. Tracheal and bronchial compression with rapidly progressive symptoms may occur[74] and may present a difficult challenge to the anaesthetist.[21]

Lung parenchyma

Intrapulmonary neurofibromas are rare, usually asymptomatic and carry a good prognosis. However, they may grow to a large size resulting in cough and dyspnoea. Excision of such tumours is advocated as they carry a risk of malignancy.[96] The association of pulmonary fibrosis and NF1 has long been recognized although estimates of its incidence of 10–20%[17] have probably been overstated. More recent surveys[45] have suggested that the association may even be coincidental. However, reports suggest that the typically bilateral upper lobe pulmonary fibrosis is of adult onset and is progressive,[9 87] and the resulting restrictive defect may culminate in pulmonary hypertension and right ventricular failure.[97] In addition, cystic lung disease may co-exist[63] as a honeycomb lung structure or large apical cysts.[65] Although rare, pneumothorax has been reported.[101]

Chest wall deformities

Thoracic spinal curvatures are common in NF1 and affect approximately 10% of NF1 patients. They appear early in childhood and often require corrective surgery.[2] Dystrophic spinal curvatures are short and sharp and progress throughout life. Severe kyphosis, although uncommon, may be associated with tumours and a high risk of neurological deficit. Scoliosis with rotation may also occur and produces a reduction in lung volume, which if severe, may result in respiratory failure. Although pectus excavatum and carinatum occur in up to 30% of patients with NF1,[81] they do not contribute to respiratory problems. Neurofibromas and schwannomas may produce erosion of the ribs and are a rare cause of flail chest.[40]

It is clear that evaluation of the respiratory system is an essential part of the pre-operative management of patients with NF1, and as well as chest x-ray, may include CT evaluation of the thorax and detailed lung function testing.

Cardiovascular system

Although hypertension is the most commonly occurring cardiovascular manifestation of NF, the disease may also primarily affect the myocardium and the vasculature.

Hypertension

Hypertension occurs in approximately 6% of NF1 patients and may be multifactorial. In the majority of cases, essential hypertension coincidentally coexists with the condition; however, in 30% of cases the hypertension is secondary to renovascular disease,[43] aortic coarctation or phaeochromocytoma.

Hypertension presenting in the young NF1 sufferer is usually because of renal artery stenosis, which may be bilateral.[8] The arterial lesions are of variable morphology with fusiform intimal narrowing, or nodule or aneurysm formation.[88] Surgery to stenosed vessels may be disappointing, possibly as the vessel abnormalities extend to intrarenal tissue. However, success has been reported with percutaneous angioplasty, resulting in remission of hypertension.[32] Regular arterial pressure measurement is thus a vital screen in even young patients with NF1 and mandatory in the pre-operative assessment of these patients. Caution should be taken when treating hypertension with potentially renotoxic drugs.

A recent review of the literature suggests that phaeochromocytoma affects between 0.1–5.7% of patients with NF1 but almost 25% of patients with phaeochromocytoma have the disease.[64] The mean age of presentation in NF1 patients is 42 yr and most patients have solitary, non-malignant tumours. The tumours are more commonly seen in association with other neurocutaneous syndromes such as the Von Hippel-Lindau syndrome.[72] Sudden, short-lasting frontal or occipital headache occurs in 60% of patients while other common symptoms include anxiety attacks, weight loss, palpitations and night sweats.[84] Sustained or paradoxical hypertension that proves resistant to treatment should raise the suspicion of phaeochromocytoma and appropriate investigations such as urinary catecholamine estimation and abdominal CT scanning should be performed. It is vital to exclude phaeochromocytoma as a cause of hypertension as anaesthesia, surgery and pregnancy are particularly hazardous if it is undiagnosed pre-operatively. Death during orthopaedic surgery as a result of phaeochromocytoma has been reported in NF1 patients.[28 48] The subject of anaesthesia for the patient with phaeochromocytoma has been recently reviewed.[75]

Coarctation of the thoracic[22] or abdominal[110] aorta is a rare cause of hypertension in the NF1 patient.

Vasculopathy and cardiac pathology

In addition to the renal arterial lesions, in some cases of NF1 a generalized vasculopathy exists. Micronodular vascular proliferation may be seen in the nervous system and visceral organs: when a prominent feature, this is termed vascular neurofibromatosis. In spite of varying histological appearances, it has been proposed that the primary mechanism is that of schwann cell proliferation with secondary degeneration or fibrosis of the vessel wall. This process may result in formation of both aortic and cerebral aneurysms.[85]

Although initial studies suggested congenital heart defects were more common in the NF1 population,[71] a subsequent review[56] found no clear evidence of a link.

Idiopathic hypertrophic cardiomyopathy has been reported in NF1[25 86] but doubt exists as to whether this is a coincidental finding in two conditions that have a similar incidence. Fitzpatrick[31] suggests that the left ventricular hypertrophy may be secondary to neurofibromatosis and because of the abnormal metabolism of catecholamines or nerve growth factor, or that both diseases represent defects of neural crest tissue. In addition, neurofibromas may involve the heart causing both hypertrophy and outflow obstruction;[77] the development of an endocardial fibromuscular band giving rise to right ventricular failure has also been described.[83]

The presence of coronary artery aneurysms has been documented[15] and may represent a vascular manifestation of the disease; coronary vasospasm has been associated with sudden death in such a patient.[38]

Superior vena caval obstruction resulting from large mediastinal tumours is well recognized in NF1[74] and vascular lesions involving the subclavian artery may result in life-threatening haemothorax.[66 99] A high index of suspicion is required to diagnose the involvement of mediastinal structures and radiological examinations may need repeating at frequent intervals to exclude significant intrathoracic tumours.

The autonomic nervous system is not immune to the condition and sudden death has been reported in a patient with neurofibromatosis who was found to have a neurofibroma of the vagus nerve.[11]

It is clear that careful questioning concerning cardiovascular disease coupled with appropriate investigations is an integral part of the assessment of the patient with neurofibromatosis.

Central nervous system

As tumours of the central nervous system account for the major portion of the morbidity and mortality of patients with neurofibromatosis, it is unsurprising that patients often present for cranial or spinal neurosurgery. Anaesthesia for such patients follows normal neuroanaesthetic practice although surgery to plexiform neurofibromas may result in severe haemorrhage.

Anaesthetic assessment of such patients should take into account the increased incidence of epilepsy, learning difficulties and the possibility of undiagnosed CNS tumours. Clinicians should be open to the possibility of multiple lesions and not necessarily attribute new symptoms to a pre-existing tumour. Fatal neurogenic pulmonary oedema has been reported in a child with NF1 with unsuspected cerebral involvement when undergoing spinal surgery.[103]

Although an uncommon manifestation of NF1, cerebrovascular disease has been reported and probably represents similar pathology of vascular structures as described earlier. The most common disorder is a progressive narrowing of the internal carotid artery at the origin of the anterior and middle cerebral arteries.[95] Although it is not clear that there is an increase in the incidence of cerebrovascular accident in NF1 patients once the risk factor of hypertension is excluded, symptomatic ischaemic disease has been reported and confirmed by cerebral angiography. Furthermore, cerebral aneurysm formation has been reported and affects both the anterior and posterior circulations.[89] Control of arterial pressure perioperatively must be carefully considered in the light of arterial occlusive disease and the potential presence of aneurysms.

In addition to the respiratory pathology described above, involvement of brainstem structures by neurofibroma or glioma may result in central hypoventilation syndromes which may require respiratory support even in childhood.[91] Such patients may exhibit protracted weaning from mechanical ventilation post-operatively.

Gastrointestinal and genitourinary systems

Gastrointestinal tumours in NF1 may present with disordered gut motility, abdominal pain, haematemesis or melaena; although neurofibromas, usually affecting the jejenum or stomach, are the most common lesions, leiomyoma, ganglioneuroma and sarcoma have been described. All may result in intestinal perforation.

Gastrointestinal symptoms may be the first manifestation of neurofibromatosis.[33]

Carcinoid tumours have been described in NF1 and authors agree that the association is not coincidental. Fernandez[29] has suggested that neurofibromas and carcinoid tumours in NF1 have a common neuroendocrine origin, and this is supported by a case in which an intestinal neurofibroma showed histological transition into a carcinoid tumour.[4]

An unusual feature of the carcinoid tumour occurring in NF1 is the predilection for the duodenum and especially the ampulla of vater—an uncommon site in the non-NF1 population.[18] Patients may present with jaundice or upper gastrointestinal haemorrhage or obstruction; often, by the time a diagnosis is reached, metastases are present in the liver. The subsequent release of vasoactive peptides may result in patients presenting with the carcinoid syndrome of flushing, diarrhoea, bronchoconstriction and right heart lesions. Anaesthesia and surgery may be hazardous in this situation. Perioperative management of patients with carcinoid syndrome has been comprehensively reported by Veall.[104] It is important to note that carcinoid tumours and phaeochromocytoma may co-exist and, therefore, patients with phaeochromocytoma require imaging of the duodenum to exclude pathology in this region.[111]

The genitourinary tract may be involved in NF1 and retroperitoneal neurofibromas may result in ureteric obstruction and hydronephrosis. Similarly, bladder outflow obstruction has been reported[92] and bladder catheterization may be difficult.

Pregnancy

Although neurofibromatosis appears to have no intrinsic effect on fertility, a high rate of spontaneous abortion and stillbirth has been reported.[24,112] There is little documentation of difficult or obstructed labour because of uterine or vaginal neurofibroma but pre-term labour may occur in up to 30% of patients.[36] Pregnancy is often associated with an increase in the number and size of dermal neurofibromas and the potential for rapid increase in the size of CNS tumours must be considered.

Hypertension occurs commonly in pregnant NF1 sufferers[98] and arterial pressure must be carefully monitored throughout pregnancy. Both phaeochromocytoma and renal artery stenosis may present during pregnancy, perhaps with a lethal outcome.[42] Furthermore, renal artery stenosis may be induced by pregnancy when it may be associated with the haemolysis, elevated liver enzymes and low platelets (HELPP) syndrome.[37]

Anaesthesia for the pregnant patient with neurofibromatosis is not well documented. In the majority of patients with mild disease, the question of regional versus general anaesthesia is the same as that for patients without neurofibromatosis. In those patients with more extensive disease, regional techniques may be more appropriate, especially if airway problems are present. However, regional anaesthesia may be technically difficult if spinal neurofibromas or scoliosis are present. In addition, the presence of raised intracranial pressure must be excluded before regional anaesthesia is considered, even if this requires CT scanning with its radiation risk.[23] Anaesthesia for phaeochromocytoma in pregnancy carries its own particular difficulties.[39]

Pharmacology

There have been many reports suggesting an increased sensitivity of patients with NF1 to non-depolarizing neuromuscular blocking drugs.[6,61,62,69,70,114] In addition, the sensitivity to succinylcholine has been reported as increased,[61,62,114] decreased[6] or normal.[62,69] However, these reports are marred by a paucity of detail preventing a definite diagnosis of neurofibromatosis to be established; in addition, with the exception of one study,[6] no neuromuscular monitoring was performed. A large retrospective study of patients given succinylcholine and/or a variety of non-depolarizing neuromuscular blocking drugs with neuromuscular monitoring excluded any definite abnormal response to the relaxants given.[82] It was concluded that patients with neurofibromatosis react in a normal fashion to neuromuscular blocking drugs. However, patients with neurofibromatosis should have neuromuscular transmission monitored when neuromuscular blocking drugs are used. This is especially pertinent in NF1 patients with renal impairment or those on concurrent medication (e.g. anticonvulsant drugs), which may interfere with the normal pharmacokinetics or pharmacodynamics of neuromuscular blocking drugs.

Conclusion

The neurofibromatoses are a group of conditions that vary in their severity but which have fundamental implications for the anaesthetist, physician and surgeon. NF1 is one of the most common genetically transmitted diseases and anaesthetists with a general practice are likely to encounter patients with the condition. Although the manifestations of NF1 are often mild, there may be associated pathology of direct relevance and importance to the anaesthetic management of patients with the disease. It is therefore important to have a working knowledge of the clinical manifestations of the disease (Table 3) so that a systematic approach to the pre-operative assessment of these patients can result in rational perioperative management.

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Intrapartum epidural catheter migration: a comparative study of three dressing applications

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We compared three types of catheter fixation application for their ability to minimize the incidence and magnitude of epidural catheter movement during labour. Patients were randomized to have their epidural catheter secured by a Tegaderm dressing (group T; n=35), a Tegaderm dressing plus filter-shoulder fixation (group F; n=39), or a Niko Epi-Fix dressing (group N; n=37). The length of catheter visible at the patient's skin surface was recorded (to the nearest 0.5 cm) after insertion and before removal; the difference was defined as 'catheter movement'. Outward movement of the catheter was greatest when a Niko Epi-Fix was used (P<0.01). Concerning minimization of displacement of the epidural catheter *per se*, only a Tegaderm dressing with additional filter-shoulder fixation proved more effective than using a Niko Epi-Fix dressing (P<0.05).

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Once an epidural catheter has been safely inserted, it may still migrate appreciably despite efforts to secure it at the skin surface.[1] Such movement of the epidural catheter may induce complications many hours after insertion. Unintentional intravenous injection of local anaesthetic[2] and total spinal anaesthesia[3] have been reported during labour and attributed to catheter migration. A 'mobile' epidural catheter may enter the subdural space,[4] generating potentially dangerous effects. The catheter can exit the epidural space via an inter-vertebral foramen[5] giving rise to a patchy or unilateral block. Alternatively, it may retract into the soft tissues of the back, resulting in failure of analgesia. Movement of the catheter at the skin surface does not translate to migration of the catheter tip, but does suggest that it may have become displaced. Notable migration of the epidural catheter at the skin surface has been observed to occur in >40% of parturients.[6] We conducted a randomized controlled trial comparing three types of catheter fixation application for their ability to minimize the incidence and magnitude of epidural catheter migration during labour.

Methods and results

After obtaining approval from the Regional Ethics Committee, 135 women requesting epidural analgesia during labour were invited to participate and written informed consent was obtained from each.

The epidural catheter was inserted using an 'Epidural minipack' kit (SIMS Portex Ltd, Hythe, UK), with the patient in the sitting position. After identifying the epidural space by loss of resistance to 0.9% saline, a 16G Portex epidural catheter was inserted, leaving 4 cm within the space. The remainder of the catheter was directed longitudinally up the patient's back in the midline, over their left shoulder and the in-line filter was attached. Once inserted, one of following three dressing methods was randomly allocated using a sealed envelope technique in order to secure the catheter. In group T, a 10×25 cm Tegaderm dressing (3M Health Care, St Paul, MN, USA) was applied over a single redundant loop of catheter. In group F, the catheter was secured exactly as in group T, but in addition, the in-line epidural filter was fixed to the skin of the left shoulder by Mefix (Molnycke Health Care AB, Goteborg, Sweden). In group N, a Niko Epi-Fix dressing (Niko Surgical Ltd, Stonehouse, UK) was applied to the site of catheter insertion. The design of this fixative allows no redundant loop of catheter. Lengths of 10 cm width Mefix were applied to all of the borders of the respective Tegaderm and Niko Epi-Fix dressings. A length of 5 cm

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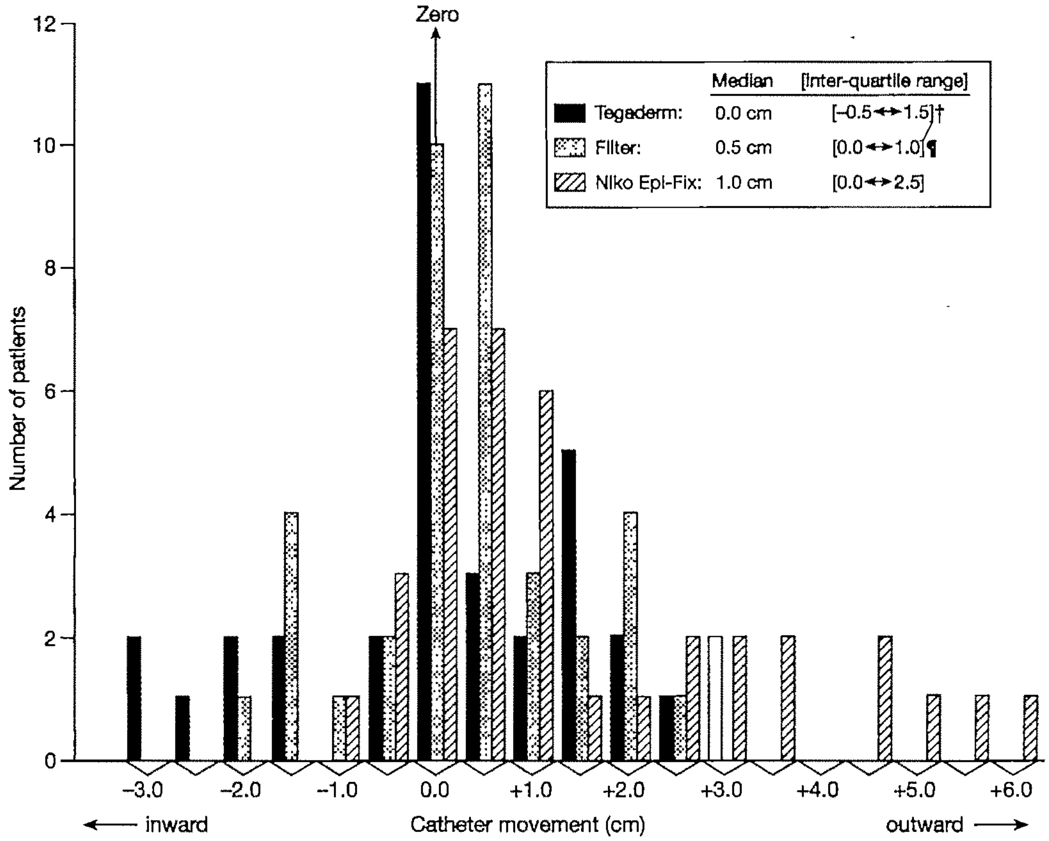

Fig 1 Histogram showing directional catheter movement classified by type of dressing. †Significantly different from Niko Epi-Fix (P<0.01); ¶significantly different from Niko Epi-Fix (P<0.01).

width Mefix was applied over the exposed catheter, from the upper border of the respective dressing superiorly along the patient's back. The in-line filter was connected to a Graseby 9300 infusion pump (Graseby Medical Ltd, Watford, UK) via an extension set. Epidural analgesia was effected by continuous infusion (10–15 ml h^{-1}) of 0.1% bupivacaine and 0.001% alfentanil. Patients did not ambulate during labour, but were allowed to adopt either sitting or lateral positions.

Following dressing application, the patient characteristics were recorded and the time was noted. The inter-vertebral space at which the epidural was sited, the use of a skin incision, the distance between the skin and the epidural space (cm), and the length of catheter visible at the skin surface (to the nearest 0.5 cm) were also recorded.

One hour after delivery, immediately before removing the epidural catheter, the time was noted, allowing the duration of the catheter's presence to be calculated. Also recorded were the integrity of the dressing, whether any analgesia problems had been encountered and the length of catheter visible at the skin surface (to the nearest 0.5 cm).

The initial catheter reading minus the final measurement was defined as the catheter movement. Two aspects of catheter movement were considered. The first follows a convention adopted by previous workers,[2] in which movement of the catheter can occur in a outward (+) or inward (−) direction, and was defined as 'directional' movement (MOV_D). The second addresses only the magnitude of catheter displacement, irrespective of direction, and was defined as 'absolute' movement (MOV_A).

Based on previous data,[1] 35 patients per group were required to detect an inter-group difference of 0.5 cm (α 0.05, β 0.9). Data were analysed using analysis of variance and Dunnnett's *post hoc* test, Student's t-test, χ^2 analysis and Pearson's correlation coefficients where appropriate (SPSS v.9.0).

Of the 135 patients recruited, 24 were not completely assessed because of progression to emergency Caesarean section. Of the remaining 111 patients, 35 were in group T, 39 in group F and 37 in group N. Six patients who experienced complete failure of analgesia with no demonstrable sensory block had final observations recorded and their epidural catheter resited. Five of these patients were in group N and one in group T (P<0.05; χ^2). There were no differences in patient characteristics, duration of catheter presence (P>0.05; analysis of variance) or final dressing integrity (P>0.05; χ^2) between groups. The use of a blade for skin incision, or choosing a different inter-vertebral space did not influence MOV_D or MOV_A (P>0.05; Student's t-test). There was no significant correlation between duration of catheter presence and MOV_D or MOV_A.

No movement of the epidural catheter was observed in 28 patients, whilst inward movement was seen in 21 and outward in 62. Directional catheter movement (MOV_D) for the three dressing groups is shown in Figure 1, with associated values for median and inter-quartile range. Patients in groups T and F had less 'directional' movement than those in group N ($P<0.01$: analysis of variance). Only patients in group F displayed less MOV_A than those in group N ($P<0.05$: analysis of variance).

In patients in group F, MOV_A of the epidural catheter tended to be higher in those of greater body mass index ($R=0.27$; $P<0.01$). No significant correlation was identified between MOV_A (groups T and N), or MOV_D (any dressing group), and the patient's body mass index.

Comment

The ideal method of fixing catheters would encompass optimal security of the catheter, ease of inspection and maintenance of sterility at the site of insertion. Not only must an application function in dry conditions, but it must retain this efficacy after exposure to blood, perspiration and epidural solution. Placement of a Tegaderm over a loop of catheter (group T) is the routine method of catheter fixation in our hospital. Fixation of a particulate filter (group F) was undertaken to examine whether this stabilized the catheter further. The Niko Epi-Fix (used in group N) is a fixation device that has been introduced recently, specifically for securing an epidural catheter. The cost of this device is comparable to that of the Tegaderm dressing (£1.50 and £1.24 respectively; September 2000).

Outward movement of the epidural catheter was greatest when a Niko Epi-Fix dressing was used to secure the catheter, and was associated with significantly more failures in analgesia. However, when attempting to minimize movement of the catheter irrespective of direction, only the Tegaderm dressing with additional filter fixation confers a significant advantage over the Niko Epi-Fix.

We identified no correlation between epidural catheter movement and the duration of catheter presence, a finding in concordance with earlier work.[6] Additionally, we showed that neither the use of a small skin incision at the site of catheter insertion, nor the selected inter-vertebral level affected movement of the epidural catheter. A previous study[1] demonstrated that body mass index is related to amount of catheter movement. Our data confirmed this association in group F but was unable to show this in the remainder of the patients, perhaps because inadequate numbers of people were studied.

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Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine

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Sixty-two women requesting regional analgesia in labour were allocated to receive a 1.5 ml intrathecal injection as part of a combined spinal–epidural (CSE) analgesic technique. This contained either bupivacaine 2.5 mg plus fentanyl 25 μg (group F) or bupivacaine 2.5 mg plus diamorphine 250 μg (group D). Times of analgesic onset and offset were recorded, motor and proprioceptive assessments made and side-effects noted. Analgesic onset was not significantly different between the groups (group F, 8.0 min; group D, 9.5 min; $P=0.3$) but time to first top-up request was significantly longer in the diamorphine group (group F, 73 min; group D, 101 min; $P=0.003$). Motor loss, assessed by the modified Bromage score, was statistically but not

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clinically greater in the fentanyl group (P=0.01). Maternal hypotension, pruritis, proprioceptive loss, nausea and fetal bradycardia were rare and not severe, and their incidences did not differ between groups. No respiratory depression was observed after CSE. This use of diamorphine was not associated with increased side-effects compared with fentanyl/bupivacaine, and it has a longer duration of action.

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The combined spinal–epidural (CSE) technique for initiation of mobile analgesia in labour is now used widely in obstetric anaesthetic practice. It is said to offer the advantages of rapid onset of analgesia via the spinal route with the flexibility of epidural top-ups later in labour or for obstetric procedures. We decided to investigate the possibility of replacing the intrathecal fentanyl usually used with diamorphine to attempt to prolong the analgesic effect without increasing the incidence of side-effects.

Methods and results

Local ethics committee approval was granted for this study. Over a 3 month period, all women attending our delivery suite in labour and requesting epidural analgesia were informed about the project. Sixty-two women were recruited. All had singleton pregnancies, were at more than 36 weeks of gestation and had a cephalic presentation. Those who had received opioids within 4 h were excluded.

After i.v. access had been secured, the epidural was sited at L2/3 or L3/4 with the patient sitting. Patients were allocated to one of two groups: group F received isobaric bupivacaine 2.5 mg plus fentanyl 25 µg, total volume 1.5 ml (n=32); group D received isobaric bupivacaine 2.5 mg plus diamorphine 250 µg, total volume 1.5 ml (n=30). The appropriate mixture was injected intrathecally through a 26 G Whitacre needle using a needle-through-needle technique. Cerebrospinal fluid aspirates were tested before and after injection, and the time of injection was noted. The attending midwife was unaware of the group allocation. Pulse, blood pressure and cardiotocograph recordings were carried out as normal.

The times to the first comfortable contraction (freedom from pain regardless of block height; t_1) and to first top-up request (t_2) were recorded by the midwife. Patients were told to inform their midwife as soon as the pain of contractions recurred. Maternal hypotension (systolic blood pressure less than 90 mm Hg or a reduction of more than 20 mm Hg from baseline or symptomatic), nausea, vomiting, pruritis and fetal bradycardia (less than 100 beats min^{-1}) were recorded and treated if necessary. Proprioception and lower limb power were assessed 30 min after injection using hallux positioning and modified Bromage scoring respectively. All patients were observed every 4 h for 24 h after treatment for evidence of respiratory depression. A respiratory rate greater than 9 b.p.m. was taken as adequate. All subsequent top-ups were opioid-free (0.2% ropivacaine 10–15 ml) to avoid worsening any potential respiratory depression resulting from the intrathecal opioid.

The two groups were similar in terms of age, parity and induction and augmentation rates. Cervical dilation was similar in the two groups (group D, mean 4.0 cm, five patients >5 cm dilated; group F, mean 4.1 cm, seven patients >5 cm dilated). Two women were withdrawn from group D (one analgesic failure, one delivery) and one from group F (analgesic failure). Results from the remaining 59 patients were analysed using the t test, the χ^2 test, the Mann–Whitney U-test and the Kruskal–Wallis test as appropriate. The results are summarized in Table 1. A P value less than 0.05 was taken as significant.

Our results show a clear increase in time to first top-up request in group D compared with group F, with no significant difference in onset times. All episodes of fetal bradycardia were transient and required no treatment. All three episodes of maternal hypotension resolved with 500 ml of crystalloid and, in one case, a 6 mg bolus of ephedrine. Pruritis was more common with fentanyl, but only one patient of the five with pruritis required treatment with i.v. naloxone 200 µg. There were no instances of nausea or vomiting requiring treatment. Proprioceptive deficits were uncommon in both groups but modified Bromage scores revealed significantly greater motor loss in the fentanyl

Table 1 Results for groups D and F. Data for t_1 and t_2 are mean (SD). Proprioception data are numbers of patients failing x out of 8 attempts (x=0, 1–3, ⩾4). Modified Bromage score data are numbers of patients in each scoring category (0, 1, 2, 3). *Significant at (P<0.05)

	Group F (n=31)	**Group D** (n=28)	P
t_1 (min)	8.0 (4.5)	9.5 (6.0)	0.30
t_2 (min:s)	73:29	101:36	0.003*
Pruritis (n)	4	1	0.13
Fetal bradycardia (n)	3	5	0.14
Maternal hypotension (n)	1	2	0.22
Proprioception	27, 4, 0	23, 5, 0	0.36
Modified Bromage score	18, 9, 4, 0	24, 4, 0, 0	0.01*

group. There were no cases of respiratory depression detected in the 24 h after drug administration in either group.

Comments

This study shows that the use of 250 μg diamorphine, when compared with fentanyl 25 μg, given intrathecally with bupivacaine 2.5 mg does not produce a significant increase in side-effects and carries benefit in terms of prolongation of analgesic action. The onset time is similar in the two groups, the difference being 1.5 min or at most one contraction. A difference was noted in power assessment statistically, but clinically all patients were able to mobilize safely.

The CSE is a technique commonly used to initiate labour analgesia. There is ongoing debate in the literature about whether the benefits offered by this approach to the labouring woman above those seen with a low-dose epidural outweigh the perceived small increase in risk associated with deliberate dural puncture.[1–6] This argument has yet to be resolved, but it is clear that an increase in the duration of action of the initial dose results in less breakthrough pain during labour, a factor registered as important in studies of maternal satisfaction.[7] The ultimate aim may be a single-intervention method of complete analgesia throughout childbirth, and our study indicates a possible step in the right direction. Decreasing the need for top-ups and associated medical/midwifery interventions may also result in a decrease in staff workload.

The dose of diamorphine used in this study was deliberately low because of worries regarding side-effects, principally pruritis and respiratory depression. Diamorphine was chosen in place of morphine because of its much higher oil/water partition coefficient (morphine 1.4, diamorphine 280, fentanyl 816).[8] Doses of 500 μg diamorphine alone have been reported for intrathecal labour analgesia without respiratory depression occurring.[9] Morphine has been reported to cause delayed respiratory depression and even apnoea with doses as low as 1 mg intrathecally,[8 10] and thus, as a dose of 1–2 mg is reported to be necessary for significant benefit,[10 11] it cannot be used reliably and safely in labour. Although we have found no evidence of respiratory depression with diamorphine 250 μg intrathecally, we have not proved conclusively that it will never occur. Care must always be taken in the post-delivery monitoring of these patients.

Recent studies have shown effective analgesia with doses of intrathecal opioid lower than those commonly used.[12] It may be that the prolongation of action seen with diamorphine requires less than this 250 μg dose. It may also be that this extension of time to first top-up is increased with a higher intrathecal dose. It seems likely that we have detected an enhanced bupivacaine-sparing effect and that extension of this effect is dependent on local anaesthetic concentration at the effector site combined with improved or prolonged spinal opioid receptor stimulation. To what degree further extension of time to first top-up is possible remains to be elucidated, as does the minimum dose of diamorphine required to produce this effect.

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Small-dose selective spinal anaesthesia for short-duration outpatient gynaecological laparoscopy: recovery characteristics compared with propofol anaesthesia

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A randomized controlled trial compared recovery characteristics after selective spinal anaesthesia (SSA) or propofol general anaesthesia (GA) for short-duration outpatient laparoscopic surgery. Forty women were randomized to receive either SSA (1% lidocaine 10 mg, sufentanil 10 µg and sterile water 1.8 ml) or GA (propofol and nitrous oxide 50% in oxygen). Compared with the GA group, times to leaving the operating room, performing a straight leg raise, performing deep knee-bends and achieving an Aldrete score >9 and the time in Phase II recovery were significantly shorter ($P<0.05$) in the SSA group.

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Spinal anaesthesia in outpatients is currently struggling to compete with the newer general anaesthetic agents, because of prolonged discharge times.[1–5] Selective spinal anaesthesia (SSA) has been defined as 'the practice of employing minimal doses of intrathecal agents so that only the nerve roots supplying a specific area and only the modalities that require to be anaesthetised are affected'.[4] Dorsal column and motor functions are essentially preserved with SSA, such that patients are able to ambulate at the end of surgery.[6]

This prospective randomized study compared recovery characteristics after SSA with those after propofol general anaesthesia (GA) for outpatient gynaecological laparoscopy.

Methods and results

The study had ethics approval from the University of British Columbia. After written consent, 40 women (ASA I) scheduled for outpatient gynaecological laparoscopic surgery were randomized into two groups (SSA or GA) by means of coded envelopes. An i.v. line was established and paracetamol 975 mg p.o. was administered 30–45 min before surgery. Routine monitors (ECG, automatic blood pressure and pulse oximetry) were applied in the operating room and the patients were anaesthetized.

GA group

General anaesthesia was induced with propofol 2 mg kg^{-1}. Tracheal intubation was facilitated with mivacurium 0.15 mg kg^{-1}, and fentanyl 2 µg kg^{-1} was administered for intra-operative analgesia. Anaesthesia was maintained with propofol 100 µg kg^{-1} min^{-1} and nitrous oxide 50% in oxygen. The propofol infusion was titrated between 100–150 µg kg^{-1} min^{-1} to maintain a minimally acceptable depth of anaesthesia (i.e. to maintain haemodynamic variables within 15% of baseline values). The lungs were ventilated to maintain end-tidal carbon dioxide between 32 and 36 mm Hg. Boluses of mivacurium 0.04 mg kg^{-1} were administered with the aim of maintaining at least one twitch using a train-of-four monitor. Propofol was discontinued when the laparoscope was removed and nitrous oxide after the last suture. No neuromuscular reversal agents were required.

SSA Group

With the patient in the sitting position, a 25 G Whitacre spinal needle was inserted at L3–4 or L4–5. The orifice of the spinal needle was placed cephalad and the spinal solution was injected rapidly. The test solution consisted of 1% lidocaine 10 mg (1 ml; AstraZeneca, Mississauga,

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Table 1 Post-operative outcomes. Values are mean (SD). $^{*}P<0.002$; $^{**}P<0.05$

	GA	SSA
Recovery time (min)		
Time to awaken	11 (8.3)	0
Extubation	11.2 (8.6)	0
Orientation	12.6 (8.4)	0
Times from end of surgery to (min)		
Exit theatre	11.9 (6.5)	6.0 (2.2)*
Straight leg raise	32.4 (17.9)	3.8 (2.4)*
Deep knee bend	76.1 (35.6)	3.8 (2.4)*
Aldrete score >9	51.0 (35.2)	6.7 (1.8)*
Late recovery times (min)		
PACU stay	79.1 (26.8)	75.8 (38.0)
Phase II stay	30.4 (16.5)	20.3 (5.6)**
Total Phase I + II stay	109 (31.6)	96.2 (38.6)

Canada), sufentanil 10 μg (0.2 ml) and sterile water (1.8 ml). This solution had a specific gravity of 1.002 (CSF=1.0069).[2] Patients remained sitting for 1 min, after which they were allowed to lie down, and the operating room table was placed in reverse Trendelenburg position for 6–8 min to facilitate cephalad spread of the hypobaric spinal anaesthetic. During this time, the patients were also prepared for surgery. Before insufflation of the abdomen, the table was returned to the horizontal position. Three to four litres of carbon dioxide was insufflated before insertion of trocars. Shoulder tip discomfort was treated with fentanyl 25–50 μg. Midazolam 1–2 mg was administered for anxiolysis if required. Supplementary oxygen was administered for oxygen saturation <93%.

In both groups, at the end of laparoscopy, perphenazine 1 mg i.v. was given for anti-emesis, port site infiltration with bupivacaine 0.25% was performed to minimize incisional pain, and diclofenac 100 mg PR was administered for post-operative analgesia.

Recovery times were determined at 1 min intervals from discontinuation of nitrous oxide (coincident with the last suture) to awakening (opening eyes to command); orientation to day, place and person; and subsequently at 15 min intervals until the patient had achieved the unit's discharge criteria.[2] Postanaesthetic Aldrete scores were noted at the same intervals. Assessments of operating conditions were made by the surgeon on an ordinal scale (poor, good, excellent).

Observations in the postanaesthetic care unit (PACU) were made by research staff or recovery nurses. Patients in both groups were discharged from the PACU to the Phase II area after meeting the unit's discharge criteria.[2] The incidences of post-operative side-effects and the durations of stay in the PACU and Phase II unit were also recorded.

Statistical analysis was performed with the Number Cruncher Statistical System computer program, version 5.03 (Graph Pad Software, San Diego, CA, USA). Continuous data are expressed as mean (standard deviation); between-group comparisons were performed with two-sample *t*-tests. A value of $P<0.05$ was considered significant.

The two groups were similar with respect to patient characteristics and the type and duration of surgery (15–20 min). Surgical conditions were rated good to excellent in most patients in both groups. One patient in the SSA group was converted to GA because of technical difficulties resulting in the loss of some spinal anaesthetic solution during injection and an inadequate block. Six patients in the SSA group experienced shoulder-tip discomfort, and three of these required treatment with fentanyl (≤50 μg). Midazolam for anxiolysis was required in five patients in the SSA group and the maximum dose did not exceed 2 mg.

Post-operative outcomes are summarized in Table 1. Times to leaving theatre, straight leg raising, deep knee bending and achieving an Aldrete score of <9 and time spent in the Phase II stay unit were significantly less in the SSA group. Twelve patients in the SSA group reported post-operative pruritus compared with none in the GA group ($P<0.05$).

Comment

The role of spinal anaesthesia in outpatients is being subjected to increasing scrutiny.[1 4] In a study examining factors affecting discharge times in outpatients, Pavlin and colleagues[3] demonstrated that patients who received conventional-dose spinal anaesthesia had significantly longer discharge times (202–213 min) than those who were managed with GA (184–185 min).

In an effort to address this dilemma, our centre has attempted to study the role of SSA in the outpatient laparoscopy model.[2 4–6] Initial studies demonstrated that recovery with SSA was faster than conventional-dose subarachnoid block,[2] and dorsal column and motor function were found to be preserved with SSA.[5 6] This study has demonstrated that SSA is a reasonable alternative to GA in terms of recovery profile and operating conditions, and it opens up the possibility of SSA as an alternative to general anaesthetics in selected patients. However, more data from other centres using SSA for other procedures is required before SSA can be presented to patients as a viable alternative for outpatient surgery.

This study has demonstrated a potential weakness in the Aldrete score as a measure of recovery because even though patients in the GA group achieved an Aldrete score >9, they were unable to perform deep knee bends until much later, probably as a result of the combined effects of propofol, opioids and muscle relaxants. Our study suggests that the Aldrete score needs to be validated as a measure of fast-track eligibility by using other yardsticks and other tests of balance and motor function. Unless such a validation is performed, there seems little logic in fast-tracking a patient to a Phase II area if they are unable to perform basic motor tests that are a prerequisite for ambulation.

In conclusion, this study demonstrated that the use of selective spinal anaesthesia (SSA) as an alternative to propofol for the maintenance of GA for short-duration outpatient gynaecological laparoscopy was associated with shorter times to achieve certain milestones of recovery. Future studies need to address the safety of bypassing the PACU after SSA and the feasibility of performing other surgical procedures with SSA.

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Analgesic efficacy of tramadol 2 mg kg^{-1} for paediatric day-case adenoidectomy

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We studied the analgesic efficacy of tramadol 2 mg kg^{-1} for post-operative analgesia after day-case adenoidectomy in children aged 1–3 yr. Eighty children were allocated randomly to receive tramadol 2 mg kg^{-1} i.v. or placebo immediately after induction of anaesthesia. Anaesthesia was induced with alfentanil 10 μg kg^{-1} and propofol 4 mg kg^{-1} followed by mivacurium 0.2 mg kg^{-1} for tracheal intubation. Anaesthesia was continued with sevoflurane in nitrous oxide and oxygen. All children were given ibuprofen rectally at approximately 10 mg kg^{-1} before the start of surgery. Post-operative pain and recovery assessments were performed by a nurse blinded to the analgesic treatment using the Aldrete recovery score, the pain/discomfort scale and measurement of recovery times. Rescue medication (pethidine in increments of 5 mg i.v.) was administered according to the pain scores. A post-operative questionnaire was used to evaluate the need for analgesia at home up to 24 h after operation. Rescue analgesic at home was rectal or oral ibuprofen 125 mg. Children in the tramadol group required fewer pethidine doses than those in the placebo group (P=0.014). Forty-five per cent of children receiving tramadol did not require post-operative analgesia at all compared with 15% of children receiving placebo (P=0.003). Recovery times and the incidence of adverse effects were similar in the two groups in the recovery room and at home. The requirement for rectal ibuprofen at home did not differ between groups.

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Pain is a common sequela after adenoidectomy both in hospital and at home.[1] Commonly, intraoperative non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol are used to control post-operative pain, but their analgesic effect is often insufficient. Opioids provide effective analgesia but fear of their side-effects, especially respiratory depression, emesis and sedation, have restricted their use in day-case anaesthesia.

Tramadol has a low affinity for opioid receptors but also exerts its effect by direct modulation of central mono-aminergic pathways. In children over 1 yr, tramadol was well tolerated and an effective analgesic after operation, with adverse effects similar to those of other opioids.[2] Because of its negligible effect on respiration[3] it may offer an advantage over traditional opioids for relief of post-operative pain in day-case surgery. Although tramadol has been used extensively in the adult surgical population, its role in paediatric day-case surgery, especially in the 1–3 yr age group, remains to be evaluated further. Therefore, we designed this double-blind, placebo-controlled parallel-group study to determine the efficacy of tramadol 2 mg kg^{-1} as an adjuvant to a traditional dose of rectal ibuprofen (10 mg kg^{-1}) for post-operative pain control after day-case adenoidectomy in small children. We especially sought to evaluate its effect on the speed and quality of recovery.

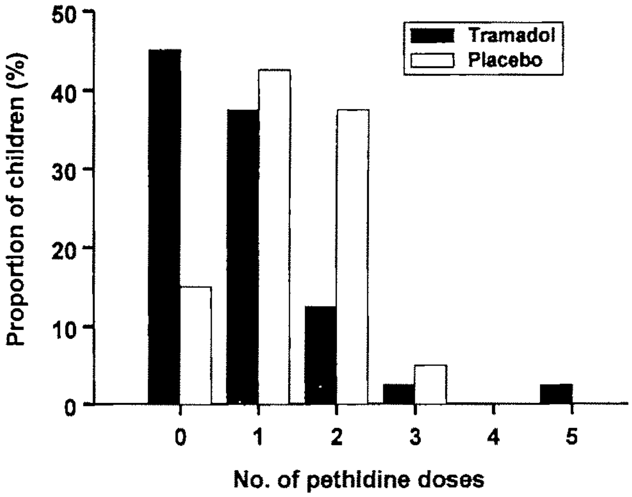

Fig 1 Number of pethidine doses required in the recovery room in the tramadol and placebo groups (P=0.014).

Table 1 Recovery times (min) in the two study groups [mean (SD, 95% confidence interval)]. No differences between groups

	Tramadol	**Placebo**
Recovery of spontaneous ventilation	2.7 (1.4, 2.3–3.2)	2.8 (1.8, 2.3–3.4)
Emergence	23 (7, 21–26)	25 (9, 22–28)
Time to first dose of pethidine	25 (8, 22–29)	25 (12, 21–29)
Parental arrival in the recovery room	27 (9, 24–30)	27 (8, 25–29)
Ambulation	101 (34, 91–112)	94 (31, 85–105)
Discharge criteria fulfilled	113 (34, 103–124)	108 (28, 99–118)

Methods and results

After obtaining approval from the local hospital ethics committee and written informed consent from parents, we studied 80 children, ASA I–II, aged 1–3 yr, undergoing day-case adenoidectomy. No premedication was used. General anaesthesia was induced with i.v. alfentanil 10 µg kg^{-1} and lidocaine 10 mg followed by propofol 4 mg kg^{-1} and mivacurium 0.2 mg kg^{-1}. According to a computer-generated table of random numbers, each child was allocated randomly to receive i.v. either tramadol 2 mg kg^{-1} (Tramal; Grünenthal GbmH, Germany) diluted in 2 ml of saline (n = 40) or placebo (saline 2 ml) (n=40) during a 10 min period immediately after tracheal intubation. Both study drugs were prepared and administered by a nurse who did not otherwise participate in the care of the child. All patients were also given rectal ibuprofen 125 mg (approximately 10 mg kg^{-1}) before the start of surgery. Anaesthesia was maintained with 2–4% sevoflurane and 70% nitrous oxide in oxygen with controlled ventilation. Standard monitoring was used throughout anaesthesia.

In the recovery room, the recovery of the children and the need for rescue analgesia were assessed by a trained nurse who was blinded to the analgesic treatment used. Pain was assessed using the three objective components (crying, movement and agitation) of the pain/discomfort scale of Hannallah and colleagues,[4] each variable scoring 0–2 points (best to worst). If the child was in pain (pain score >3), i.v. pethidine was administered in increments of 5 mg every 5 min until the child was comfortable. The time to administering the first dose and the total amount of analgesic needed were recorded. Any post-operative adverse effects were recorded. Recovery of the child was assessed with the Aldrete scoring system and by measuring predetermined recovery times. The criteria for discharge were: fully awake, stable vital signs for at least 30 min, no bleeding, no signs of excessive pain, no vomiting, and able to ambulate according to age.

At home the rescue analgesic was always rectal or oral ibuprofen 125 mg, which was supplied to the parents upon discharge. The parents of the children were asked to record, using a post-operative questionnaire, the well-being (pain, use of ibuprofen, vomiting, tiredness, sleep) of the child at home until 24 h after anaesthesia.

Analyses were performed using Students' t-test, the Mann–Whitney U-test and the χ^2 test as appropriate. Values are expressed as mean (SD) and 95% confidence interval or number (%). P<0.05 was considered significant. Group size was calculated on the basis of detecting a 30% decrease in pethidine consumption, to give 80% power and significance of 0.05. A minimum of 38 patients was required in each group.

The two groups were comparable in age, weight, duration of anaesthesia and surgery. The mean (SD) rectal dose of ibuprofen was 10.1 (1.6 and 1.7) mg kg^{-1} in the tramadol and placebo groups respectively. Children in the tramadol group required fewer pethidine doses than those in the placebo group (P=0.014) (Fig. 1). Eighteen (45%) children receiving tramadol did not need a rescue analgesic as opposed to 6 (15%) receiving placebo (P=0.003). Seven (18%) children receiving tramadol and 17 (43%) children receiving placebo needed at least two doses of pethidine post-operatively (P=0.005). The mean (SD) dose of pethidine administered was 4.12 (5.1) mg kg^{-1} in the tramadol group versus 6.6 (3.9) mg kg^{-1} in the placebo group (P=0.002). Aldrete recovery scores and all recovery times were similar in the two groups (Table 1). Post-operative airway problems (desaturation, laryngospasm) occurred in an equal number of patients in the two groups. One child (3%) receiving tramadol vomited in the recovery room. At home ibuprofen was given to 22 (59%) and 28 (74%) children in the tramadol (n=37) and placebo (n=38) groups respectively (not significant). Vomiting occurred in five (15%) children with tramadol and two (5%) children with placebo (not significant). There were no differences between groups in drinking ability, tiredness, bad temper or quality of sleep.

Comment

Because of its relative lack of sedative action and respiratory depression,[3] tramadol has been a subject of keen interest as an alternative to traditional opioids for post-operative pain control. However, in many adult studies, data on the efficacy and optimal dose of tramadol in producing adequate pain relief after surgery have been conflicting. Fewer studies have been done in the paediatric population, in which it has been shown to be beneficial for post-operative pain control when administered in varying doses and by different routes.[2 3 5]

The recommended dose of tramadol for children is 1–2 mg kg^{-1} three or four times daily (package insert). We chose to use 2 mg kg^{-1} as this dose has been shown to be more efficacious than 1 mg kg^{-1}, with no increase in adverse events.[3] Forty-five per cent of the children in our study who received tramadol did not need a rescue analgesic in the recovery room. However, although this difference was significant compared with placebo, 55% of the children still required additional analgesia in the immediate recovery period. In adults, the optimal initial dose of tramadol would appear to be 3 mg kg^{-1} for acute pain of moderate to severe intensity. The pharmacokinetics of i.v. tramadol in children has only recently been investigated, and it appears that children require the same body weight-related doses as adults.[6] Therefore, it is possible that children also need a higher initial bolus dose of tramadol for effective pain relief. Whether higher doses of tramadol improve analgesia without increasing adverse events in the paediatric population warrants further investigation.

Although 55% of the children receiving tramadol still needed pethidine in the recovery room, the total amount of pethidine required was significantly reduced compared with the placebo group. Only 18% of children in the tramadol group required at least two doses of pethidine compared with 43% in the placebo group. This opioid-sparing effect of tramadol and its apparent lack of sedative effect[3] may have been the reason for the equally rapid recovery in both study groups and, in our opinion, emphasizes the advantage of tramadol in day-case surgery.

The overall incidence of adverse events with tramadol in the 1–3 yr age group was low. Even the concomitant use of another opioid (alfentanil) during anaesthesia in our study, which would have been expected to increase the opioid effects of tramadol, did not delay the return of spontaneous ventilation or increase post-operative vomiting compared with placebo. Our findings are in accordance with the study by Bösenberg and Ratcliffe, who reported a similar low incidence of post-operative nausea and vomiting in older children with tramadol 2 mg kg^{-1}.[3] These investigators also demonstrated only minor respiratory depression with tramadol during spontaneous ventilation with halothane.[3]

Eighty-five per cent of the children who received only rectal ibuprofen needed additional pethidine doses in the recovery room. The low efficacy of ibuprofen in providing analgesia may have been partly a result of the slow absorption of rectal ibuprofen or an inadequate dose in some children. However, our findings confirm that NSAIDs alone are often unable to provide sufficient analgesia after adenoidectomy even when given intravenously during surgery.[1] In this respect, the intraoperative administration of tramadol may offer a useful addition to post-operative pain control after surgery.

Because of the comparatively long elimination half-life of tramadol (6.4 h) and its metabolite M1 (10.6 h) in children,[6] we expected it to reduce the need for analgesia at home. However, although the number of children given ibuprofen at home during the first 24 h after surgery was lower in the tramadol group (59% versus 74% in the placebo group) the difference did not reach statistical significance. The incidence of children requiring analgesia at home is consistent with the findings of Nikanne and colleagues[1] on post-operative pain after adenoidectomy, and confirms the importance of regular analgesic treatment on the first few days after surgery.

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Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass

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We set out to determine if the heparinase-modified thrombelastogram using anticoagulated blood from patients during cardiac surgery could guide treatment with haemostatic components. In 60 patients a simple algorithm predicted a possible 60–80% decrease in the use of haemostatic components. In a second series, 30 patients were allocated to receive components using this intra-operative algorithm and 30 using clinical criteria and laboratory-based tests. Ten patients in the clinical group received a total of 16 units of fresh frozen plasma and nine platelet concentrates compared with five patients transfused with five units of fresh frozen plasma and one platelet concentrate in the algorithm group. Twelve-hour chest tube losses [algorithm group 470 (295–820) ml, clinically managed group 390 (240–820) ml (median, quartile values)] were not different between groups despite the threefold reduction in the use of haemostatic products, showing that intra-operative monitoring of coagulation in the anticoagulated patient can be used to guide treatment.

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Haemostatic blood components contribute significantly to the overall transfusion burden in patients having major surgery and especially cardiac surgery.

The thrombelastogram measures the rate and strength of clot formation.[1] Initiation of clot formation is defined as the reaction or r-time and the strength of the clot by the maximum amplitude of the trace. During cardiopulmonary bypass, the heparinase-modified thrombelastogram will develop despite anticoagulation with heparin in doses of 300 IU kg^{-1} and gives the same results as those obtained using blood when heparin has been antagonized with protamine.[2]

Previous reports[3 4] have described algorithms that reduce the need for haemostatic blood component therapy and re-exploration. However, these studies waited until microvascular bleeding occurred before starting testing and intervention.

In this pilot study we investigated the predictive value and use of an algorithm using thrombelastogram measurements made during heart surgery using anticoagulated blood. The principal end-point for efficacy was reduced total exposure to haemostatic component therapies.

Methods and results

We studied two groups of 60 patients, who gave consent to the study. Ten per cent of the patients in each group had a heart transplantation and were taking aspirin and/or

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Table 1 Decision tree for administration of haemostatic components based on the heparinase-modified Celite-activated thrombelastogram (TEG) at time 2. The range of normal values in Celite-activated blood for r is 10–14 mm and the maximum amplitude (MA) should be more than 56 mm. FFP=unit(s) of fresh frozen plasma. Lys$_{30}$ = (MA–trace amplitude 30 min later) × 100

Intra-operative TEG variable	Implication	Therapy
r > 14 mm < 21 mm	Clotting factors mildly reduced	1 FFP
r > 21 mm < 28 mm	Clotting factors moderately reduced	2 FFP
r > 28 mm	Clotting factors severely reduced	4 FFP
MA <48 mm	Moderate in platelet number/function	1 platelet pool
MA <40 mm	Severe decrease in platelet number/function	2 platelet pools
lys$_{30}$ >7.5%	Increased lysis (this was not observed)	Aprotinin

warfarin immediately before surgery. About 50% of the patients in each group had revascularization and were also taking aspirin, and required multiple grafts with a bypass time estimated to be greater than 100 min. The remaining 40% of the patients were having the Ross procedure, multiple valve or valve and revascularization surgery. No patients were having repeat operations and none received prophylactic aprotinin, epsilon aminocaproic or tranexamic acid.

The study plan allowed data from patients who returned to theatre for the control of surgical bleeding or who died within 48 h of the surgery to be discarded and replaced by measurements from an additional patient allocated to the same group. Three patients in the first series of patients and two in the second series (one each in the algorithm and control groups) returned to theatre. All these patients had drain losses of >400 ml h^{-1} and a thrombelastogram result within the normal range. No patient died during the first 48 h after operation.

Patient details were not significantly different between groups but showed a wide distribution of values for age (21–83 yr) and bypass time (48–167 min).

We made standard thrombelastogram measurements (TEG®; Haemoscope Corporation, Niles, IL, USA) in 360 µl of whole blood activated with 1% Celite. Samples were taken and analysed at the following times. (i) Baseline, after induction of anaesthesia. This sample was to exclude any pre-operative coagulopathy. (ii) Bypass. This sample was taken during rewarming when the bypass system venous blood temperature was ≥35°C, or within 30 min of separation from bypass in patients when tepid bypass was used (nasopharyngeal temperature ≈34°C). The sample was developed in a cuvette containing heparinase. The result was used to define the need for haemostatic components using the algorithm shown in Table 1. (iii) Ten to fifteen minutes after protamine. The thrombelastogram was developed with and without heparinase, to detect any residual heparin effect. Some of this blood was sent for laboratory measurement of prothrombin time, activated partial thromboplastin time (APTT), platelet count and fibrinogen concentration.

No patient had an abnormal thrombelastogram before surgery (sample 1) and there was no difference between measurements made at sample times 2 and 3, confirming previous data.[2] No patient showed a residual heparin effect in paired samples at time point 3. The results were available within 20 min. Laboratory tests of coagulation, fibrinogen and platelet count typically took 70–90 min to perform and report.

Statistical and power analysis was performed using GB-Stat™ version 6.5 for Macintosh (Dynamic Microsystems, Silver Spring, MD, USA) on a PowerMac. Statistical differences between groups were defined using the χ^2 test.

Series one

In the first 60 patients, haemostatic treatment (fresh frozen plasma and platelets) was determined using criteria obtained from conventional laboratory tests (prothrombin time and/or APTT ratio >1.5 times control, platelet count <50 000 dl^{-1}, fibrinogen concentration ≤0.8 mg dl^{-1}) in the presence of microvascular bleeding (>400 ml in the first hour after surgery or >100 ml h^{-1} for four consecutive hours). We noted the number of component units actually given, and the amount predicted from the thrombelastogram algorithm. This was done so that the method could be used to estimate the likely reduction in component transfusion, and to define the size of sample in the subsequent series after power analysis.

On the basis of clinical assessment and laboratory tests, 22 of 60 patients received blood components. If we had used the treatment algorithm, the number of patients receiving component therapy would have been seven ($P<0.05$). The predicted number of components used (six units of fresh frozen plasma and two pools of platelets) would have been significantly less than the 38 units of fresh frozen plasma and 17 platelet pools actually transfused in these 60 patients ($P<0.05$).

Power analysis suggested that 27 patients per group would be required to demonstrate a fourfold reduction in component use with an α of 0.05 and a power of >90%.

Series two

In the second part of the study, 60 patients were randomly allocated to have products ordered and administered on the basis of either the algorithm (group T) or the wishes of the clinician (group C). Patients were allocated to groups by means of a series of sealed envelopes. Haemostatic products were ordered and given as soon as test results were known, or as judged clinically by the surgeon or anaesthetist responsible for the case. The amounts of products given and volumes of chest drainage 6 and 12 h after surgery were recorded.

Ten of the 30 clinically managed patients received blood components according to clinical assessment and/or laboratory test results, compared with five of 30 managed by thrombelastogram data ($P<0.05$). The amount of product use in group T (five units of fresh frozen plasma and one pool of platelets) was significantly ($P<0.05$) less than the 16 units of fresh frozen plasma and nine platelet pools given to the 30 patients in group C.

Chest tube losses [median (lower and upper quartiles)] were not different between groups despite the fourfold difference in the use of haemostatic products. Twelve-hour losses were 470 (295, 820) in the group managed with the thrombelastogram and 390 (240, 820) in the group managed clinically.

Comment

The thrombelastogram has developed as a bedside monitor of the coagulation process over the past 15 yr. The device was first popularized by Dr Kang and the group in Pittsburgh for monitoring during hepatic transplantation,[5] mainly because the device detects clot lysis, which is the principal haemostatic defect in this operation.

Others in the USA found the thrombelastogram useful for cardiac surgery, in which coagulopathy has different causes compared with hepatic surgery. In the presence of microvascular bleeding, thrombelastography was better than conventional tests of coagulation in defining the abnormality and in guiding treatment.[6] Abnormal formation (principally r-time) implied reduced clotting factors, and reduced maximum amplitude deficiency implied reduced platelet numbers or function. A later study showed that this device reduced blood transfusions and also re-exploration for bleeding, which decreased fourfold during the study period.[3] Other centres reported that the maximum amplitude, measured after protamine administration, was related to early losses from post-operative drains.[4 7] This device has also been used in obstetric,[8] trauma[9] and peripheral vascular[10] practice. In all these reports the patients' blood was not anticoagulated at the time of the analysis and the test was being used to characterize rather than to predict and anticipate a coagulation abnormality.

The pilot study described here is the first to show that a heparinase-modified thrombelastogram in anticoagulated blood can predict, and reduce substantially, the need for haemostatic products without increasing post-operative bleeding in patients having heart surgery.

There are a number of potential concerns and weaknesses in the present study.

The first is related to the magnitude of the observed effect. We studied patients who were considered at high risk of requiring haemostatic products but in whom prophylactic drug therapies, such as aprotinin, would not be universally appropriate. Haemostatic components were given to about 30% of our control group patients, which is the same proportion reported from Montreal[11] and New York.[4] The second of these reports showed the benefit of an algorithm when microvascular bleeding was established. The authors described a four- to fivefold reduction in the use of frozen plasma, and our study supports this finding. In contrast to this earlier report,[4] the present study demonstrates a statistically significant, eightfold reduction in platelet transfusion, suggesting that assessment of coagulation before the observation of microvascular bleeding can be valuable.

Part of this improvement may be related to the time the components are given. The algorithm we used allowed treatment shortly after the antagonism of heparin action by protamine. In contrast, the delay in obtaining laboratory data meant that patients in the control group received their component therapy after transfer to the intensive care unit. It is obvious that the magnitude of any benefit would be less for operations in which there is less need for haemostatic components.

Secondly, we did not want to use prophylactic drug therapies such as aprotinin and tranexamic acid, as they have different effects on thrombelastography. In particular, the r-time is prolonged by aprotinin therapy and shortened by tranexamic acid.[12]

This leads to the third weakness of the present algorithm and other algorithms,[4] which is that the numerical values for each thrombelastogram parameter are based on reference ranges found in a standard population. There are no current data to show that the values chosen, or the treatment these values indicate, are optimal for any particular patient group. This is highlighted by the difference in the predicted requirement for transfusion of haemostatic components between the first and second cohorts despite similar patient characteristics, the same team of anaesthetists and surgeons, and very similar actual transfusions using conventional clinical criteria.

Finally, if the algorithm predictions were wrong, then the patients in group T might have had increased bleeding after the bypass. However, the accuracy of the prediction is not known as in neither group did we completely withhold products to determine any association with increased bleeding and the need for re-exploration. The values used in this algorithm may need modification to allow additional benefits and improve their applicability. This would require a larger, appropriately powered, multicentre study.

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Circulating tetrahydrobiopterin concentrations in patients with septic shock

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Nitric oxide synthase requires tetrahydrobiopterin for its activity. In animal models of sepsis, changes in circulating tetrahydrobiopterin concentrations precede increases in nitrate. We measured plasma tetrahydrobiopterin and nitrate concentrations on three consecutive days in 10 patients with septic shock and 10 critically ill control patients. Total nitrate concentration was measured after reduction of nitrite to nitrate. Tetrahydrobiopterin concentrations were measured using HPLC. The median (range) APACHE II score was 22 (13–27) in the patients with septic shock and 25 (7–28) in the control group. The nitrate concentration was significantly higher in patients with septic shock than in controls (P=0.01) on all days but did not change with time. Tetrahydrobiopterin concentrations were highest in the patients with septic shock on day 1 only (P=0.037). In the seven patients with renal failure, both nitrate and tetrahydrobiopterin concentrations tended to be higher than in the 13 patients without renal failure. The nitrate concentration correlated with tetrahydrobiopterin concentration on day 1 only (P=0.05). In patients with septic shock, both tetrahydrobiopterin and total nitrate concentrations were higher than those in critically ill controls but were increased mainly in patients with renal failure. In summary, tetrahydrobiopterin concentration increases during septic shock, in line with increases in nitrate concentration. However, as for nitrate, concentrations

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are affected by renal function. Measurement of tetrahydrobiopterin concentration is extremely technically demanding and time consuming and offers no advantage over measurement of nitrate concentration.

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Nitric oxide is synthesized from L-arginine by the action of nitric oxide synthase (NOS) and NOS enzymes require tetrahydrobiopterin for catalytic activity.[1] Nitric oxide is important in the maintenance of vasodilator tone and arterial pressure and it has been suggested that cytokine-mediated circulatory shock is caused by activation of the inducible isoform (type II) of NOS.[2] In biological systems, nitric oxide decomposes to nitrite and nitrate. Cytokine-mediated increases in concentrations of nitrite/nitrate are found in cell cultures. Circulating nitrite and nitrate concentrations also increase in patients with sepsis[3] and increased NOS activity in leucocytes from these patients has been demonstrated.[4] However, nitrite and nitrate are excreted by the kidney, so plasma and urine concentrations of these compounds are highly dependent upon renal function.[3] Tetrahydrobiopterin bioavailability has an important role in the regulation of nitric oxide production. In an animal model of sepsis, increased circulating biopterin concentrations preceded increases in nitrate and mirrored changes in arterial pressure.[5] The authors suggested that tetrahydrobiopterin concentrations in plasma may be a more helpful biochemical marker of the onset of septic shock than nitrite/nitrate concentrations. We investigated the use of tetrahydrobiopterin concentrations as an early biochemical marker of septic shock, compared with plasma nitrite/nitrate concentrations.

Methods and results

Patients

Following Ethical Committee approval and informed assent from a close relative, 10 patients admitted to the intensive care unit who were within 12 h of fulfilment of the inclusion criteria for septic shock, as recommended by the Consensus Meeting of the American Thoracic Society and the American Society of Critical Care Medicine, were investigated. These criteria are: clinical suspicion of infection, plus tachycardia, tachypnoea or a requirement for mechanical ventilation, hyper- or hypo-thermia and, in addition, mean arterial pressure of <90 mm Hg or a requirement for vasopressors. The APACHE II score was calculated. Ten critically ill patients with similar scores were recruited on the same day as each septic patient to provide a control group. These were non-infected patients, comprising predominantly aortic aneurysm repair and trauma patients.

Methods

Blood samples from indwelling arterial lines were obtained on day 1, and 24 and 48 h later. Blood was centrifuged and frozen at –80°C. Plasma total nitrate concentration was measured spectrophotometrically using Greiss reagent after reduction of nitrite to nitrate. Tetrahydrobiopterin concentrations were measured using high-performance liquid chromatography (HPLC) after selective oxidation with iodine. Samples were added to acid iodine solution containing 0.5% iodine and 1% potassium iodide in 0.2 M trichloroacetic acid (tube A) and to 2 M sodium hydroxide and alkaline iodine solution (1% iodine and 2% potassium iodide in 0.1 M sodium hydroxide) (tube B) and incubated for 1 h at room temperature in the dark. To the alkali tube (A) only, 1 M hydrochloric acid was then added and both were centrifuged at 10 000 *g*. Excess iodine was removed by adding freshly made 1% ascorbic acid. Under acid conditions, all pterins are converted to fluorescent biopterin, whilst under alkali conditions, tetrahydrobiopterin is converted to non-fluorescent material, with only biopterin detected. Tetrahydrobiopterin can therefore be measured as the difference between biopterin concentration under acid and alkali conditions, using HPLC with fluorescent detection.

Biopterins were separated on a C18 Techsil reverse phase column (HPLC Technology, Macclesfield, Cheshire, UK) with 10% HPLC-grade methanol in water as mobile phase, and calibrated against biopterin which had also undergone acid/alkali oxidation. Biopterin was detected fluorimetrically (excitation at 350 nm, emission at 440 nm). The accuracy of the technique was 78.3 (77.0–79.8)% in recovery experiments (n=30), using biopterin 30 ng ml^{-1} in the presence of bovine serum albumin 1 mg ml^{-1} to mimic plasma protein content. The within-run and between-run precision of the assay was 1.8% and 8.1%, respectively (n=10).

Statistical analysis

Results are expressed as median (range). Statistical analysis was performed using Microsoft Analyse-it statistical add-in for Excel for Windows. Data sets were compared using Mann Whitney *U*-test/Friedman analysis of variance, and correlations were assessed using Kendall's rank correlation. A *P* value of <0.05 was considered statistically significant.

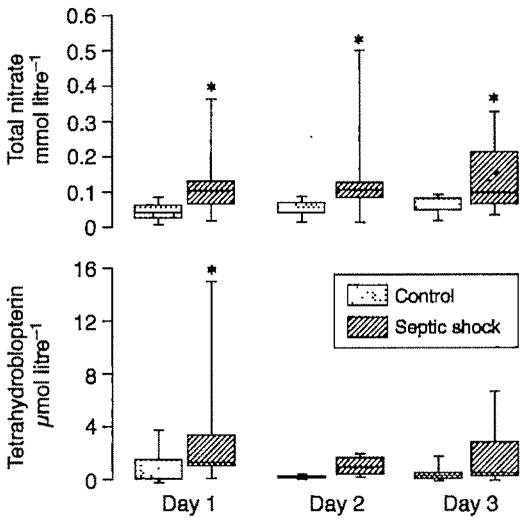

Fig 1 Plasma total nitrate and tetrahydrobiopterin concentrations in 10 patients with septic shock and 10 non-septic critically ill controls. Box and whisker plots show median, 25th and 75th percentiles and full range. *Significantly different from controls ($P<0.05$).

Results

The median (range) APACHE II score was 22 (13–27) in patients with septic shock and 25 (7–28) in the non-septic control group. The median (range) total nitrate concentration on day 1 was 114.4 (18.4–417.7) µmol litre^{-1} in patients with septic shock, which was significantly higher than that in non-septic critically ill controls (38.0 (3.3–81.4) µmol litre^{-1}) ($P=0.01$, Figure 1). Tetrahydrobiopterin concentrations were also highest in the patients with septic shock on day 1 (1.2 (0–14.9) µmol/l compared with 0.16 (0–3.7) µmol litre^{-1}; $P=0.037$, Figure 1).

Seven patients had renal failure and all of these had septic shock. The median circulating nitrate concentration in patients with renal failure was 129.0 (18.5–417.7) µmol litre^{-1}, compared with 41.8 (3.3–150.1) µmol litre^{-1} in those without. The median tetrahydrobiopterin concentration in the patients with renal failure was 1.2 (0.8–14.9) µmol litre^{-1}, compared with 0.16 (0–5.8) µmol litre^{-1} in patients without renal failure.

There was no change with time over the 3 day study period. A significant correlation was found between total nitrate and tetrahydrobiopterin concentrations on day 1 only ($P=0.05$).

Comment

We have shown that, in patients with septic shock, both plasma tetrahydrobiopterin and total nitrate concentrations are greater than in critically ill patients without septic shock early after admission on to the intensive care unit. Both tetrahydrobiopterin and nitrate concentrations appear to be increased mainly in those patients with renal failure; indeed, a significant correlation was seen between these measures.

Increased production of nitric oxide in response to activation of the type II isoform of NOS to cytokines has been suggested to be responsible for the hypotension of septic shock.[2] The first step in the synthesis of tetrahydrobiopterin, which is rate limiting for nitric oxide production by type II NOS, involves the enzyme GTP cyclohydrolase I, which is co-induced by the same mediators as those which induce type II NOS synthesis. Inhibitors of GTP cyclohydrolase I downregulate type II NOS mRNA, protein and activity. GTP cyclohydrolase activity and hence tetrahydrobiopterin have important roles in the regulation of nitric oxide release. In both rabbits and rats treated with live *Escherichia coli*, increases in tetrahydrobiopterin concentration preceded increases in nitrate concentration.[5]

Although tetrahydrobiopterin concentration was increased in patients with septic shock, the increases seen may have been due entirely to the contribution of reduced renal clearance. A previous study of 21 intensive care patients found that release of D-erythro-neopterin from macrophages tended to be greatest in patients who ultimately died.[6] Although both tetrahydrobiopterin and total nitrate concentrations were higher in the patients with septic shock than in non-infected critically ill controls, we found no differences between survivors and non-survivors, although clearly our small pilot study was not designed to show such a difference.

In summary, tetrahydrobiopterin concentration is increased during septic shock, in line with increases in nitrate concentration. However, as with nitrate, concentrations seem to be affected by renal function. Measurement of tetrahydrobiopterin concentrations is extremely technically demanding and time consuming and offers no advantage over measurement of nitrate concentrations.

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CASE REPORTS

Review of management of purpura fulminans and two case reports

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Purpura fulminans (PF) is a haemorrhagic condition usually associated with sepsis or previous infection. Features include tissue necrosis, small vessel thrombosis and disseminated intravascular coagulation. Gram-negative organisms are the commonest cause of the acute infectious type, which is often associated with multi-organ failure. An idiopathic variety, however, is often confined to the skin. The mortality rate has decreased with better treatment of secondary infections, supportive care and new treatments, but it remains a disabling condition often requiring major amputations. We describe two cases and review the various treatments for this condition.

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Purpura fulminans (PF), first described by Guelliot in 1884, is a haemorrhagic condition usually associated with either benign infection or severe sepsis. Features include hypotension, disseminated intravascular coagulation (DIC) and purpura leading to tissue necrosis with small vessel thrombosis. We describe two cases and review the treatment of this condition.

Case report 1

A previously fit 5-yr-old girl was admitted to hospital with a 10-day history of a chesty cough treated with erythromycin. The evening before admission she became generally unwell. On the morning of admission she was drowsy. A rash developed on her abdomen, and spread rapidly across her trunk and thighs.

At home and during transfer to hospital she had several seizures, which were treated with rectal diazepam.

On arrival at hospital she was drowsy and irritable and had an obvious purpuric rash. She weighed 22 kg. Her heart rate was 160 min^{-1} and arterial pressure 60/35 mm Hg. A provisional diagnosis of meningococcal septicaemia was made. After taking blood for culture, she was given benzylpenicillin (200 mg kg^{-1} 24 h^{-1}) and cefotaxime (200 mg kg^{-1} 24 h^{-1}) i.v. and gelofusin 20 ml kg^{-1}. Tracheal intubation was carried out before transfer for intensive care.

After admission her rectal temperature was 38.4°C, heart rate 160 min^{-1}, arterial pressure 70/30 mm Hg and central venous pressure 14 mm Hg. She received mechanical ventilation in pressure control mode, 16 cm H_2O, PEEP 4 cm H_2O and an $F\text{I}_{O_2}$ 0.6.

The following results were obtained:

Hb 12.2 g dl^{-1}, white cell count 6.92×10^9 litre^{-1}, platelets 162×10^9 litre^{-1}, INR 2.5, APTT ratio 2.06;
fibrin degradation products 64 ng ml^{-1} (ref. <300 ng ml^{-1});
antithrombin III function 68% (ref. 80–120);
protein C (free) 51% (ref. 70–150);
protein S (free) 89% (ref. 70–150);
protein S (total) 70% (ref. 70–130);
urea 9.7 mmol litre^{-1}, creatinine 140 μmol litre^{-1};
CSF: clear and colourless, WBCs 5 mm^{-3}, RBCs 3 mm^{-3}, no organisms;
blood cultures: *Neisseria meningitidis*.

Meningococcal septicaemia was diagnosed. Treatment with benzylpenicillin and cefotaxime was continued. She

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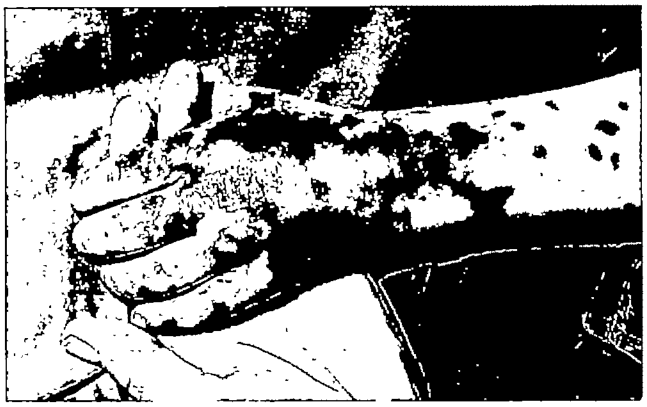

Fig 1 Purpuric lesions on the hand with characteristic clearly defined margins.

was sedated with an infusion of i.v. morphine, intermittent diazemuls and trimeprazine via nasogastric tube, and given dextrose 4% saline 0.18% at 62 ml h^{-1} i.v.

Her cardiovascular state became worse and an infusion of dobutamine and noradrenaline was started, along with i.v. hydrocortisone (20 mg kg^{-1} 24 h^{-1}). Two days later her platelet count decreased to 54×10^9 $litre^{-1}$. The white cell count was 49×10^9 $litre^{-1}$ and the prothrombin ratio increased to 3. Platelets, cryoprecipitate and fresh frozen plasma were given.

The chest x-ray showed consolidation, considered to be caused by aspiration of vomit during a fit before admission to hospital. This was treated with i.v. metronidazole (10 mg kg^{-1} 8 h^{-1}) for 5 days.

Over the following 2 days a number of ischaemic lesions developed on her toes and the tip of her left thumb. I.v. heparin (200 units h^{-1} increasing to 500 units h^{-1}) and epoprostenol (increasing to 20 ng kg^{-1} min^{-1}) were given with some improvement in her skin condition.

Four days after admission dobutamine and noradrenaline were stopped and she was extubated 4 days after that. The platelet count continued to decrease and the white cell count increased with a lymphocytosis, despite no evidence of infection. She was treated with daily fresh frozen plasma. The epoprostenol and heparin were decreased and stopped by day 10 and she was discharged to the ward the following day. Cefotaxime was discontinued after 10 days and the benzylpenicillin was changed to an oral preparation.

Four weeks after her admission she required amputation of all five toes through the proximal phalanx on her left foot, and three toes on her right.

She was discharged from hospital 6 weeks after admission, still with widespread areas of skin necrosis, mainly over the lower limbs and dorsum of the right hand. Later, de-sloughing, and grafting and excision of further necrotic areas were done, with good healing. She was later fitted with artificial toes (Figs 1 and 2).

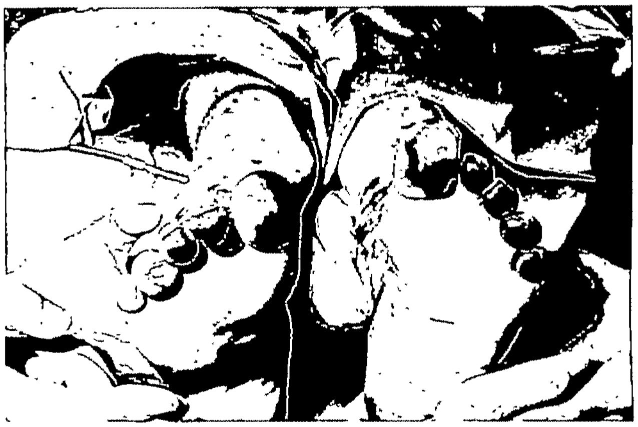

Fig 2 Necrotic toes as a result of meningococcaemia.

Case report 2

A previously fit 18-yr-old girl was admitted to hospital 10 days after developing chickenpox. The day before admission she developed dusky discolouration of both legs. Her only medication was the oral contraceptive pill.

On examination she had good circulation to the hands and feet, she was conscious and afebrile with a heart rate of 80 min^{-1} and arterial pressure of 116/80 mm Hg. She had tender bruises on both legs and thighs and knee movement was limited by pain. Examination found oral and vaginal thrush, but was otherwise unremarkable.

The following results were obtained:

Hb 13.2 g dl^{-1}, white cell count 12.4×10^9 $litre^{-1}$, platelets 65×10^9 $litre^{-1}$, INR 1.4, APTT ratio 1.2, PT ratio 2.0, fibrinogen 0.3 g $litre^{-1}$ (ref. 2–4.5 g $litre^{-1}$), fibrin degradation products 2000–5000 ng ml^{-1}, urea 13.3 mmol $litre^{-1}$, creatinine 329 µmol $litre^{-1}$;

anti-thrombin III (f) 60% (ref. 80–120);
protein C (f) 37% (ref. 70–150);
protein S (free) 41% (ref. 70–150);
protein S total 79% (ref. 70–130);
blood film: large platelets with haemangiopathic changes.

Chickenpox with PF was diagnosed. Treatment was started with fresh frozen plasma, i.v. azlocillin (100 mg kg^{-1} 24 h^{-1}), i.v. acyclovir (10 mg kg^{-1} 24 h^{-1}), oral nystatin (1 ml suspension qds), topical nystatin (one vaginal pessary daily) and topical acyclovir (vaginal cream qds).

Systemically she remained stable but she developed painful ischaemic lesions on her thighs, calves and upper limbs over the following 48 h and she was transferred to the intensive care unit for emergency plasma exchange. I.v. epoprostenol (prostacyclin) was started, increasing from 1 to 4 ng $kg^{-1}min^{-1}$. I.v. fluids were increased to achieve a urinary output of 1 ml kg^{-1} h^{-1}. Pain was treated with i.v. morphine using a patient controlled device.

The skin lesions spread to involve her flanks and hands, her white cell count increased to 28×10^9 $litre^{-1}$, and coagulation measurements and renal function deteriorated.

Plasma exchange was continued, and fresh frozen plasma given to treat 'thrombotic thrombocytopaenic purpura' and replace proteins C and S. Antithrombin III concentration was reduced and treatment with antithrombin III started.

Several digits became necrotic and an i.v. infusion of tissue plasminogen activator (t-PA) was started (0.5 mg kg^{-1} over 4 h) followed by 100 units h^{-1} of heparin. Blood analysis suggested haemolysis and blood transfusions and careful fluid monitoring were required.

By the seventh day of her intensive care unit admission she was started on i.v. ketanserin (10 mg bolus followed by 2 mg h^{-1} for 24 h) in addition to treatment with i.v. epoprostenol (10 ng kg^{-1} min^{-1}), i.v. heparin (100 units h^{-1}) and plasma exchange three to four times a week.

On day eight oral ketanserin was started (20 mg bd) and the epoprostenol reduced. On day 14 her epoprostenol was stopped and she left the intensive care unit receiving oral ketanserin, i.v. heparin, and regular plasma exchange.

Four days after discharge to the ward she had a pulmonary embolus (APTT 39 despite heparin) confirmed by radionucleide scan and treated with warfarin. Four weeks after admission she had plastic surgery and amputation of several digits.

Discussion

PF is a life-threatening disorder of acute onset characterized by cutaneous haemorrhage and necrosis caused by DIC and dermal vascular thrombosis.

Three distinct categories can be identified: inherited or acquired abnormalities of the protein C or other coagulation systems, 'acute infectious' PF and 'idiopathic'.[1]

We have described two cases of PF, one of the acute infectious variety and the other idiopathic. The idiopathic type was first recognized as an entity in 1964[2] and described as a disorder of childhood, which is preceded by a benign illness. It does, however, also occur in adults.

Inherited and acquired abnormalities of the protein C and protein S anticoagulant pathway are thought to be responsible for the majority of cases of PF, while Gram-negative organisms are the commonest cause of the acute infectious variety.[3] The idiopathic variety is uncommon and differs from the acute infectious type in that microthrombi mainly occur in skin blood vessels rather than vessels of other organs.

The most common acute infection with which PF is associated is meningococcal sepsis, and in this condition the development of PF indicates a poor prognosis.[3] Varicella is also a common association and, less commonly, pneumococcal sepsis and measles. In the neonatal period group B streptococcus appears to be the major cause but Staphylococcus, *Escherichia coli*, Enterobacter and others have been described.

Clinical features

The lesions of PF have a characteristic appearance, which distinguishes them from other purpuric lesions. Erythema is rapidly followed by irregular central areas of blue-black haemorrhagic necrosis with a surrounding erythematous border.[4] Vesicles and bullae may form. Affected areas are painful and indurated. Although initially sterile, secondary infection of gangrenous tissue may occur, contributing to late mortality and morbidity. Necrosis may extend to muscle and bone. Healing leads to scarring, and auto-amputation of digits and extremities may occur.

The idiopathic variety is largely confined to the skin and mainly involves the lower half of the body. A similar distribution is seen in those with protein C or protein S deficiency, whereas infectious necrosis often begins distally with proximal progression or diffusely over the body.

Differential diagnosis includes thrombotic thrombocytopaenic purpura, Henoch–Schönlein purpura and post-infectious thrombocytopaenic purpura, but in none of these is the skin necrosis so severe.

Laboratory findings

Typical haematological findings occur early and include low concentrations of fibrinogen, clotting factors and platelets as a result of their consumption, and prolonged prothrombin and partial thromboplastin times. Fibrinogen degradation products tend to be raised and concentrations of proteins C, S and antithrombin III reduced. Fever and leucocytosis with a left shift are common despite the absence of acute infection. The development of intravascular coagulation distinguishes PF from other forms of skin necrosis.

Pathogenesis

The pathogenesis is described as a 'Shwartzman-like' reaction, which is a necrotizing inflammatory lesion provoked by endotoxin from Gram-negative bacteria. The general picture in PF is of widespread microvascular thrombosis, the thrombi being made of fibrin with a mild inflammatory component. This differentiates it from other vasculitic skin disorders such as Henoch–Schönlein purpura and drug-induced purpura where the inflammatory component is more marked.

Management

The mortality rate of idiopathic PF has decreased considerably, mainly as a result of treatment of secondary infections but also from better supportive care and the use of other therapies. Management must be tailored to the individual and involve supportive therapy and replacement of blood products and clotting factors as appropriate.

In meningococcal septicaemia aggressive resuscitation, antibiotics and volume expansion are important for a good outcome. Correction of acid–base and electrolyte abnormalities and early use of oxygen and mechanical ventilation are helpful.[5]

Laboratory investigations that should be performed include a full blood count, PT, PTT, fibrinogen and fibrin degradation products. Whole blood and plasma supply both procoagulant and anticoagulant factors (protein C and S and antithrombin III) and rapid improvement in skin necrosis has been reported after their use.[4] Massive quantities may be needed to replace losses into infarcted skin.[6]

Prompt excision of necrotic tissue and wound closure is recommended. Patients who survive are often left with difficult wounds involving underlying muscle and bone, and a significant number of patients who survive multiple organ failure may need major amputations.[7] Escharotomies and/or fasciotomies may be indicated.[2 8] Fasciotomies should be considered early in patients with tense limbs and distal ischaemia, and should be performed on a clinical basis rather than on the basis of raised compartment pressures.[8]

Many therapies, described below, have been used to arrest the progression of the disease.

Heparin

Heparin bonds with antithrombin III to inhibit thrombus formation and consumption of coagulation factors and may reverse the development of skin necrosis.[4] Concurrent administration of fresh frozen plasma or antithrombin III may be necessary, particularly if antithrombin III concentrations are low. Difficulties arise in the clinical and laboratory monitoring of heparin where laboratory values are abnormal. Arbitrary schemes have been used such as a bolus of 4–10 000 units i.v. followed by an infusion,[9] but heparin resistance may occur. Relapse can occur if heparin is reduced or discontinued within several days of initial response.[10] There are arguments in favour of giving heparin before clotting factors are replaced, to as to avoid further thrombosis.[11] Concerns about thrombocytopaenia and bleeding, however, continue to limit its use.

Idiopathic PF often responds well to heparin and tends not to recur, while that associated with protein C deficiency or inhibition is more responsive to protein C replacement.[4]

Protein C

Protein C is a vitamin K-dependent glycoprotein with anticoagulant properties. It also has anti-inflammatory properties, which may contribute to improved survival.[5]

In meningococcaemia there is a strong correlation between the severity of acquired protein C deficiency and mortality. Early protein C infusion corrects the deficiency and restores skin perfusion.

Daily protein C concentrations can be measured and the blood level and clinical condition should determine its use. It may be given as an i.v. infusion or intermittently[12 13] and the infusion should be reduced over several days when parameters have stabilized. The optimal duration of therapy and the target plasma level of protein C, however, are unknown.

In homozygous protein C deficiency, fresh frozen plasma (8–12 ml kg^{-1}) can give effective replacement therapy.

Antithrombin III

Antithrombin III may be reduced in PF and replacement has been shown to normalize levels and reverse DIC.[14 15] High doses of antithrombin III may also compensate for decreases in levels of protein C in meningococcal PF.[14] A loading dose is generally given, followed by an infusion.

Recombinant tissue plasminogen activator (rtPA)

Concentrations of plasminogen activator inhibitor tend to be increased in PF and correlate with mortality in the acute infectious type.[16] Fibrin deposition results leading to microvascular thrombosis and multiple organ failure. PAI concentrations may decrease after treatment with antibiotics and fresh frozen plasma.[16]

RtPA induces clot specific fibrinolysis without any direct haemodynamic effect and with supposedly few bleeding complications. Its half-life is about 5 min and doses in the range of 0.25–0.5 mg kg^{-1} h^{-1} can improve peripheral perfusion.[17 18] Because the procoagulant state may continue beyond the first few hours, particularly in meningococcal sepsis, repeated infusions of rtPA may be beneficial. Concerns about haemorrhagic complications, however, tend to reserve its use for PF which has not responded to more conventional treatment.

Epoprostenol (prostacyclin)

I.v. epoprostenol is a powerful vasodilator and potent inhibitor of platelet aggregation. It has been used to treat PF from sepsis in infants and neonates at doses of 5–20 ng kg^{-1} min^{-1} without hypotensive side effects.[19] The beneficial effects of the infusion can be maintained with oral dipyridamole. Hypotension is a complication.

Topical nitroglycerin (TNG)

Severe pain can accompany PF. This may be secondary to prostaglandin release from poor tissue perfusion, with consequent sensitization of A delta and C nerve fibres.[20] TNG is metabolized to nitric oxide (NO) which produces vasodilatation. There are several reports of improved skin blood flow with topical nitroglycerin.[20 21] It is applied as a 2% paste and can be repeated every 4–6 h. Pain relief occurs within 10–30 min.[20] Reperfusion is probably by a combination of arteriolar and venous dilatation and opening collateral channels.[21]

I.v. dextran

This coats vessel walls, red cells and platelets, inhibiting cell aggregation, and can reduce sludging and spread of vascular damage. Low molecular weight dextran (mol. wt 40 000) is superior at counteracting red cell aggregation. Most of the reported responses have occurred when it has been given in combination with other treatments and it may be of use in those who fail to respond to plasma and heparin therapy.[4]

Plasmapheresis

Plasmapheresis removes circulating endotoxin, cytokines and inflammatory cell mediators and can assist in control of fluid balance, when excessive volumes of blood products may be needed. Fresh frozen plasma and cryoprecipitate as replacement fluid will increase fibrinogen concentrations and shorten PT and PTT.

Anticoagulation in fulminant PF remains controversial because of the tendency for both thrombosis and haemorrhage. Severe coagulopathy, placement of large catheters and heparinization all contribute to the risk of bleeding and demand experienced personnel in an intensive care setting.

Regional anaesthesia

Epidural sympathetic block with local anaesthetic (lignocaine 0.5%) has been reported to improve skin perfusion and reverse the development of PF. It avoids the haemodynamic instability associated with systemic vasodilators,[22] of particular benefit in those with circulatory compromise, while also providing analgesia. However, the presence of a coagulopathy and the risk of vertebral canal haematoma may contraindicate its use.

Other therapies

Epsilon aminocaproic acid inhibits fibrinolysis but has been reported to arrest skin necrosis when given alone in idiopathic PF. The mechanism is unclear and it may potentiate vascular thrombosis.

Vitamin K will normalize levels of proteins C and S in those with vitamin K deficiency but there is no clear evidence of benefit.

Ketanserin is a serotonin (S2) antagonist and a weak alpha blocker. It has been used for the treatment of intermittent claudication and Raynaud's disease,[23 24] but there is no evidence to date for its benefit in PF.

Gangrenous areas have a peripheral margin of hypoxia because of partial arteriolar occlusion and these zones may benefit from hyperbaric oxygen,[25] although there is insufficient evidence to suggest a consistent benefit in PF. Its use is restricted by the development of convulsions and bronchopulmonary dysplasia.[4]

Leech saliva contains an anticoagulant called hirudin, which is the most potent inhibitor of thrombin known and can promote local bleeding for hours. It can reverse thrombus formation in PF.[26] The high affinity and specificity of hirudin for thrombin enable it to penetrate thrombi and neutralize fibrin-bound thrombin, and to enter the extravascular space to further quench thrombin at its site of origin.[26] It may also enter the systemic circulation to reverse organ damage. Leeches may, however, introduce infection.

Glucocorticoids have often been used in idiopathic PF without evidence of benefit. Their role may be defined in the setting of PF after an allergic illness as a result of their anti-inflammatory effect, or as immunosuppressive therapy if an antibody inhibitor of protein C is present.[3]

Warfarin can reduce levels of active forms of protein C and S when given during the acute phase of PF and can, therefore, exacerbate thrombosis. It probably does not induce relapses but, as the risk of late relapse is low, there is probably no indication for long-term prophylactic therapy.

Conclusion

We have described two cases of PF, one associated with acute infection and the other of the idiopathic variety. Supportive treatment and replacement of deficient blood components, fresh frozen plasma and clotting factors is the mainstay of therapy.

Protein C and antithrombin III should be given if deficient. Heparin should be considered early on because of the risk of thrombosis with factor replacement. Dextran may have a role in complementing these treatments.

Other treatment modalities should be used depending on the progress of the disease, but there is no strong evidence in favour of one particular therapy.

Prostacyclin may cause hypotension and nitroglycerin can have unpredictable effects. Plasmapheresis may be helpful when fluid overload is a problem. There is no evidence to date regarding the benefit of ketanserin but it is a treatment option. Combination therapy is usually used.

We advise rigorous resuscitation with fluids, ventilation and inotropes, and early consideration of lower limb fasciotomies.

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Intra-operative and post-operative hypercapnia leading to delayed respiratory failure associated with transanal endoscopic microsurgery under general anaesthesia

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We present an unusual case of hypercapnia and surgical emphysema during transanal endoscopic microsurgery, which led to delayed post-operative ventilatory failure. The hypercapnia and surgical emphysema were secondary to rectal insufflation with carbon dioxide used to facilitate visualization and resection of a rectal tumour. Despite a return to wakefulness after surgery, the patient's level of consciousness deteriorated in the recovery area as a result of hypercapnia. The Pa_{CO_2} rose to 16.8 kPa because of absorption of carbon dioxide from the surgical emphysema. On close examination, surgical emphysema was identified in unusual

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areas, including the anterior abdominal wall, both loins, both groins and the left thigh. Reventilation was required until these unusual carbon dioxide stores had dissipated. We discuss the need for prolonged post-operative vigilance in patients with surgical emphysema secondary to carbon dioxide insufflation, and the risk of delayed ventilatory failure.

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Keywords: carbon dioxide, hypercapnia; anaesthetic techniques, rectal insufflation; complications, subcutaneous emphysema; complications, hypercapnia; complications, ventilatory failure

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Transanal endoscopic microsurgery (TEM) has emerged as a minimally invasive means of resecting rectal tumours which may cause less morbidity than transabdominal approaches to the rectum.[1] TEM uses an operating rectoscope consisting of a cylinder bevelled at the distal end, measuring either 12 or 20 cm in length and 4 cm in outer diameter. When in place, the instrument is sealed with a gas-tight disc through which the surgeon operates using binocular optics. Instruments are manipulated through airtight ports in this disc. Visibility is maintained by continuous rectal distension using carbon dioxide as the insufflation gas. The patient is positioned so that the lesion to be resected is lowermost, allowing the bevel of the rectoscope to face downward.

TEM avoids many of the problems associated with laparotomy, although complications have been reported. The commonest are bleeding, perforation, incontinence and rectal stricture.[2] Our case report highlights an unreported, potentially life-threatening complication: hypercapnia and ventilatory failure requiring reventilation in the post-operative period.

Case report

An 81-yr-old, 75 kg man underwent TEM for a bleeding rectal lesion that had been biopsied a month earlier under general anaesthesia. The initial procedure had been uneventful and involved a spontaneously breathing anaesthetic induced with propofol and fentanyl and maintained with isoflurane, nitrous oxide and oxygen using a laryngeal mask. No morphine was used during the perioperative period.

The patient's medical history included mild asthma controlled with inhaled beclomethasone two puffs twice a day and a salbutamol inhaler, which he used less than twice a month.

On the occasion of the TEM no pre-medication was prescribed, at the request of the patient. After pre-oxygenation, anaesthesia was induced with fentanyl 0.1 mg, propofol 150 mg and vecuronium 8 mg. The trachea was intubated and anaesthesia maintained with oxygen and nitrous oxide in a ratio of 1:2 with an end-tidal concentration of enflurane of 0.6–1.2%. During the 2.5 h of surgery, anaesthesia was supplemented with boluses of morphine and vecuronium to a total of 10 and 12 mg respectively. Standard monitoring was applied, including transcutaneous nerve stimulation.

In the operating theatre the patient was placed in the lithotomy position, then approximately 45° of Trendelenburg tilt with 20° of rotation to the patient's left side were applied to facilitate the use of the TEM equipment.

Fifty minutes into the procedure, a sudden rise in the end-tidal carbon dioxide concentration ($E'CO_2$) from 4.3 to 6.8 kPa was noted, recorded by a Datex capnograph. This coincided with a rise in peak airway pressure from 17 to 25 cm H_2O, despite no changes in tidal volume or patient position. Anaesthesia was considered to be of adequate depth and the degree of neuromuscular block was measured as one palpable twitch in a train-of-four response. The only finding on auscultation of the chest was bilateral expiratory wheeze. The bronchospasm settled after treatment with an i.v. bolus of salbutamol 250 µg with a further 250 µg infused over the following 30 min. Airway pressure returned to 17 cm H_2O and the $E'CO_2$ settled at 6.1 kPa.

For approximately 30 min, all recorded variables remained normal, then the $E'CO_2$ began to rise again. On this occasion, chest sounds were normal with no new respiratory signs. Help was sought from a senior anaesthetist. Core temperature remained normal at 36.8°C. Pulse and arterial blood pressure were within normal limits. Minute ventilation was increased from 4.9 to 9.8 litre min^{-1}, the respiratory rate from 8 to 14 b.p.m. and the fresh gas flow from 1 to 4 litre min^{-1}. The nitrous oxide was replaced by air, as there was a suspicion that there may have been an undetected pneumothorax. The enflurane was increased and the table tilt reduced to 10°. Despite these measures, the $E'CO_2$ rose to a maximum of 13 kPa during the next 30 min. Oxygen saturation was unchanged at approximately 97%, airway pressure remained less than 20 cm H_2O, breath sounds were still unchanged and the patient's temperature remained normal. The $E'CO_2$ returned to 6.1 kPa after 30 min as insufflation was progressively reduced and surgery ceased. Ventilation proceeded on oxygen and enflurane.

Residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg, with full recovery of the train-of-four response.

The patient began to breathe spontaneously and rejected the tracheal tube. He was extubated 15 min after the discontinuation of anaesthesia with an E'_{CO_2} of 4.9 kPa, blood pressure 124/56 mm Hg and heart rate 84 b.p.m., and transferred to the recovery area.

On arrival in the recovery area, the patient demonstrated activity equivalent to a Glasgow coma score of 11 (3 for eyes, 6 for movement and 2 for verbal). However, over the next 20 min his level of consciousness deteriorated. The medical staff in the recovery room administered a small dose of doxapram (20 mg) and naloxone 0.4 mg, with no response. On examination, the patient was unresponsive to painful stimuli, haemodynamic parameters were normal, no blood loss was recorded and he was breathing normally at the rate of 16–20 b.p.m. The only abnormal finding on initial examination of the chest was left-sided surgical emphysema, and a provisional diagnosis of a pneumothorax was made. Arterial blood gases were analysed and a chest x-ray was taken. Further examination of the patient revealed extensive surgical emphysema across the anterior abdominal wall, both loins, both groins and the left thigh. The chest x-ray confirmed the subcutaneous emphysema. However, there were no signs of a pneumothorax or other abnormal findings. Arterial blood gases with an FI_{O_2} of 0.6, administered by face mask, were pH 6.97, P_{CO_2} 16.8 kPa, P_{O_2} 32.7 kPa, HCO_3 29 mmol litre^{-1}, base excess –6.1. In view of the high P_{CO_2} and the altered level of consciousness, the patient was reintubated and ventilated. Propofol 50 mg and succinylcholine 75 mg were used to facilitate intubation and the patient was transferred to the intensive therapy unit (ITU).

No further sedation was given and hourly arterial blood gases were taken. Three hours after arrival on the ITU the patient was fully conscious, with a Pa_{CO_2} of 5.4 kPa, and was extubated. One hour later, with no alteration in his level of consciousness, breathing through a Hudson mask approximately 40% oxygen with a respiratory rate of 14 b.p.m., arterial blood gas analysis was pH 7.38, P_{CO_2} 5.1 kPa, P_{O_2} 13.0 kPa, HCO_3 22.5 mmol litre^{-1} and base excess –1.7. The patient returned to the ward the next day and the remainder of his stay in hospital was uneventful.

Discussion

This case illustrates the effect of iatrogenic subcutaneous carbon dioxide stores on a post-operative patient, once mechanical ventilation had been discontinued. This has not been described previously with TEM surgery.

The need for increased minute ventilation to maintain normocapnia during laparoscopic surgery is well known. Minute ventilation increases of 30%[3] and 25%[4] have been reported as necessary to maintain normocapnia. No clear recommendations for TEM are available, and the dangers of excessive absorption of carbon dioxide are not appreciated.

TEM is a technique practised in a small number of surgical centres. The anticipated problems include patient positioning and the possibility of prolonged surgery. Those not anticipated are the development of extensive subcutaneous emphysema and the hypercapnia resulting from rectal insufflation with carbon dioxide.

Post-operative hypercapnia resulting from a similar mechanism has been described after renal laparoscopic surgery.[5] The duration of insufflation, the extraperitoneal approach, the development of subcutaneous emphysema and the extent of the dissection have been shown to be important determinants of the resultant carbon dioxide absorption.

Gas under tension can track along surgically opened tissue planes to produce collections of extraperitoneal gas,[6] and we feel this is the likely origin of the subcutaneous emphysema. A flow of carbon dioxide during insufflation of up to 6 litres min^{-1} has been recommended to maintain intrarectal pressure between 12 and 15 mm Hg.[2] We suggest that insufflation flow and intrarectal pressure be monitored continually.

The carbon dioxide eliminated after insufflation is a combination of the carbon dioxide produced and that absorbed from dilated visci and surgical emphysema. The Trendelenburg/lithotomy position and the tracking of carbon dioxide to the loins, groins and thighs (areas not easily accessible to the anaesthetist interoperatively) hindered the detection of surgical emphysema in this patient. We suggest that, if unexpectedly high levels of E'_{CO_2} or Pa_{CO_2} are detected during or after procedures involving carbon dioxide insufflation, a detailed examination of the patient should be made to detect unusual sites of surgical emphysema.

In the recovery room this patient's arterial carbon dioxide concentration continued to rise from the stores contained in his surgical emphysema. This quantity of carbon dioxide eventually overwhelmed his capacity to excrete it. Blair showed that the insufflation of carbon dioxide into the subcutaneous fat of the anterior abdominal wall of anaesthetized juvenile pigs with a fixed minute ventilation causes an increase in arterial carbon dioxide and a decreased pH that may persist for a prolonged period.[6] He suggested that patients with similar problems should have repeated measurements of arterial carbon dioxide and remain in the recovery room for prolonged observation.

Our case highlights a potentially life-threatening complication produced by a mechanism similar to Blair's model. This is the first time that this has been reported in a patient undergoing TEM with rectal carbon dioxide insufflation. The dangers of absorbed carbon dioxide may be overcome by adjustments in ventilation interoperatively, but present as delayed and potentially life-threatening hypercapnia in the early post-operative period. We conclude that a patient with arterial hypercapnia or subcutaneous emphysema after the use of carbon dioxide as an insufflating gas should be observed for a prolonged period in the recovery room, with regular arterial carbon dioxide analysis to allow early intervention should ventilatory failure occur.

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Acute respiratory and metabolic acidosis induced by excessive muscle contraction during spinal evoked stimulation

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Spinal somatosensory evoked potentials (SSEPs) have been used to monitor spinal cord function during corrective scoliosis surgery. We report three cases in which direct epidural stimulation for measurement of SSEPs produced paraspinal muscle contraction, resulting in respiratory and metabolic acidosis. In two of the cases, SSEP-induced acidosis was observed even when only the first twitch of the train-of-four response was detectable after a second dose of muscle relaxant. In one of these two cases, the acidosis was abolished after a sufficient dose of vecuronium to ablate the twitch response. To prevent SSEP-induced respiratory and metabolic acidosis, we recommend that SSEPs should be measured only when profound neuromuscular blockade has been obtained.

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Keywords: monitoring, spinal somatosensory evoked potentials; complications, neuromuscular blockade; complications, acidosis

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Spinal somatosensory evoked potentials (SSEPs) are used to monitor spinal cord function and to reduce the risk of spinal cord injury during spinal surgery. SSEPs have been recorded from the epidural space or from the scalp after epidural or peripheral nerve stimulation during scoliosis surgery.[1–3] SSEPs recorded from the scalp are variable and affected by the effects of anaesthetic agents,[4] whereas those recorded from epidural catheter electrodes are almost unaffected by anaesthetic agents.[5] Adverse effects after epidural electrical stimulation are rare, so this technique is considered clinically reliable and safe.[6 7] We previously reported two cases in which direct epidural stimulation for measurement of SSEPs produced excessive paraspinal muscle contraction, resulting in respiratory and metabolic

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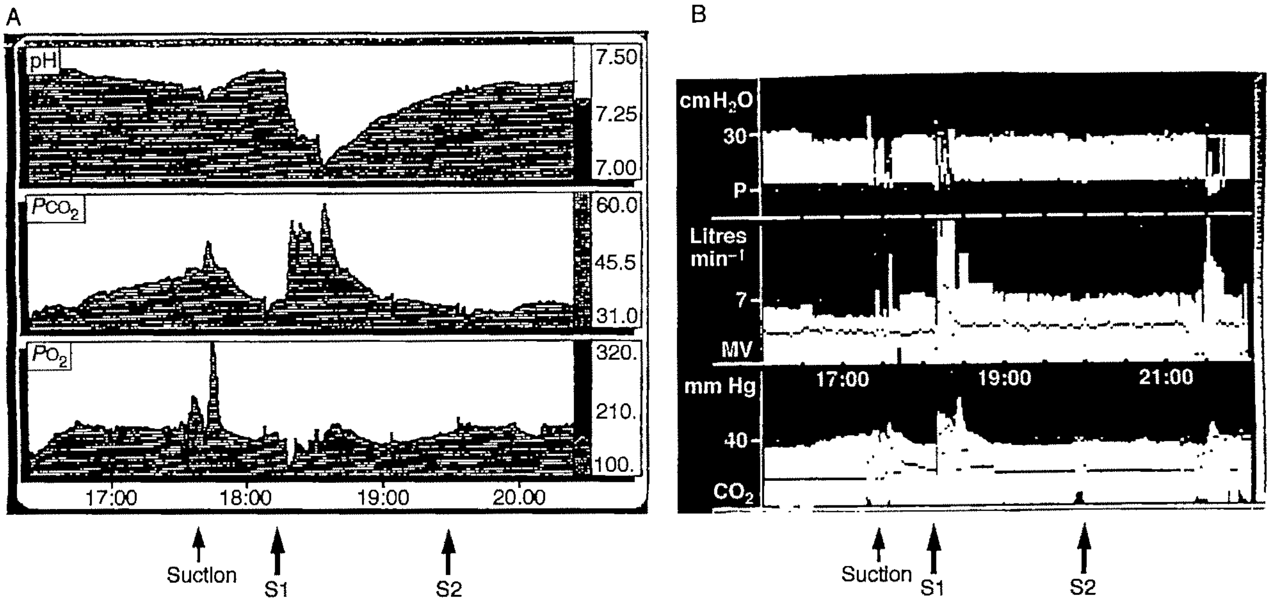

Fig 1 (A) Original trend display of arterial blood pH, Pa_{CO_2} and Pa_{O_2} recorded by continuous intra-arterial blood gas monitoring (Paratrend 7) and (B) airway pressure, end-expiratory minute volume and end-tidal carbon dioxide concentration recorded by capnography (Ultima) in case 1. Large arrows indicate direct epidural stimuli (S1 and S2). The small arrow indicates tracheal suctioning. Muscle relaxant was not given before the first stimulus (S1) but was given before the second (S2). Pa_{CO_2} increased and pH and Pa_{O_2} decreased at S1 but not at S2.

acidosis.[8] We now report the effect of neuromuscular blockade on this adverse effect.

Case reports

Case 1

A 16-yr-old, 48 kg girl with idiopathic scoliosis underwent spinal fusion with segmental spinal instrumentation. She received midazolam 2.5 mg and atropine 0.5 mg i.m. 30 min before entering the operating room. Anaesthesia was induced with thiamylal 200 mg; vecuronium 6 mg was administered to facilitate tracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen and 1.5–2.5% sevoflurane and fentanyl 1–2 μg kg^{-1} was given every hour. In order to assess motor function during surgery, a wake-up test was planned. For this test, anaesthesia was adjusted to allow the patient to move their feet according to command. Therefore no other neuromuscular blocking drugs were given during surgery. Mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4.9 and 5.3 kPa. Arterial blood gas data (FI_{O_2}=0.33) were as follows: Pa_{O_2}, 21.1 kPa; Pa_{CO_2}, 4.7 kPa; base excess (BE), –0.2 mmol $litre^{-1}$ [HCO_3^-], 23.4 mmol $litre^{-1}$; pH 7.402.

SSEPs were monitored using epidural recordings to prevent spinal cord damage resulting from manipulation of the spinal cord. The electrodes for recording and stimulation were placed directly into the epidural space at T1/T2 and L3/L4, respectively, approximately 2 h after administration of vecuronium. Since paraspinal muscle contraction was observed at a stimulus intensity of 4 mA, SSEPs were recorded using a stimulation intensity of 40 mA, a frequency of 16 Hz and a duration of 0.2 ms, but excessive paraspinal muscle contraction was observed. The systolic blood pressure increased from 13.3 to 20.0 kPa, heart rate from 78 to 110 beats min^{-1} and end-tidal carbon dioxide concentration from 4.4 to 8.0 kPa. Breath sounds and artificial ventilation did not change. There were no changes in rectal temperature or urine colour. Arterial blood gas data (FI_{O_2}=0.33) from the radial artery at this time were as follows: Pa_{O_2}, 13.7 kPa; Pa_{CO_2}, 8.4 kPa; BE, 7.1 mmol $litre^{-1}$; [HCO_3^-], 22.2 mmol $litre^{-1}$; pH 7.145. Although the patient was hyperventilated to a tidal volume of 500 ml and respiratory rate of 20 b.p.m., end-tidal carbon dioxide concentration remained high 30 min after the stimulation. Figure 1 shows the changes in the continuous intra-arterial blood gas monitoring (Paratrend 7; Biomedical Sensors Ltd, High Wycombe, UK) and end-tidal carbon dioxide concentration, peak inspiratory pressure (PIP) and inspiratory minute volume (MV) recorded by capnography (Ultima; Datex Corp, Helsinki, Finland). The intravascular sensor (Paratrend 7) was placed in the radial artery. Increases in Pa_{CO_2} and end-tidal carbon dioxide concentration and decreases in pH and Pa_{O_2} were observed immediately after the first measurement of SSEPs. Blood lactate concentrations before stimulation and 10 and 60 min after stimulation were 0.7, 4.2 and 15.2 mmol $litre^{-1}$, respectively. Vecuronium 0.1 mg kg^{-1} was given to produce complete neuromuscular block after the stimulation. Five minutes after administration of vecuronium, a second stimulation (40 mA, 16 Hz, 0.2 ms) was performed (S2 in

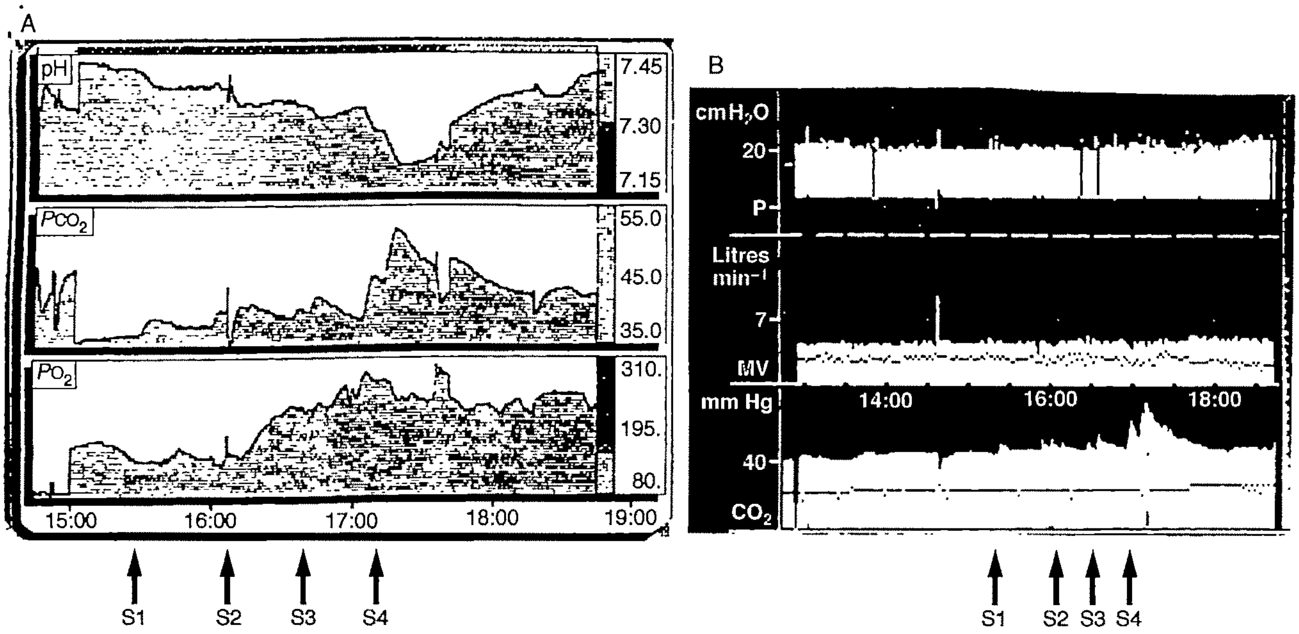

Fig 2 (A) Original trend display of arterial blood gas analyses recorded by Paratrend 7 and (B) capnogram recorded by Ultima in case 2. Large arrows indicate direct epidural stimuli (S1–S4). Vecuronium was given before S1, S2 and S3, but slight paraspinal muscle contractions were observed. Only slight changes in pH, Pa_{CO_2} and end-tidal carbon dioxide concentration were observed. When SSEPs were unexpectedly applied, however, significant changes in all these parameters were observed (S4).

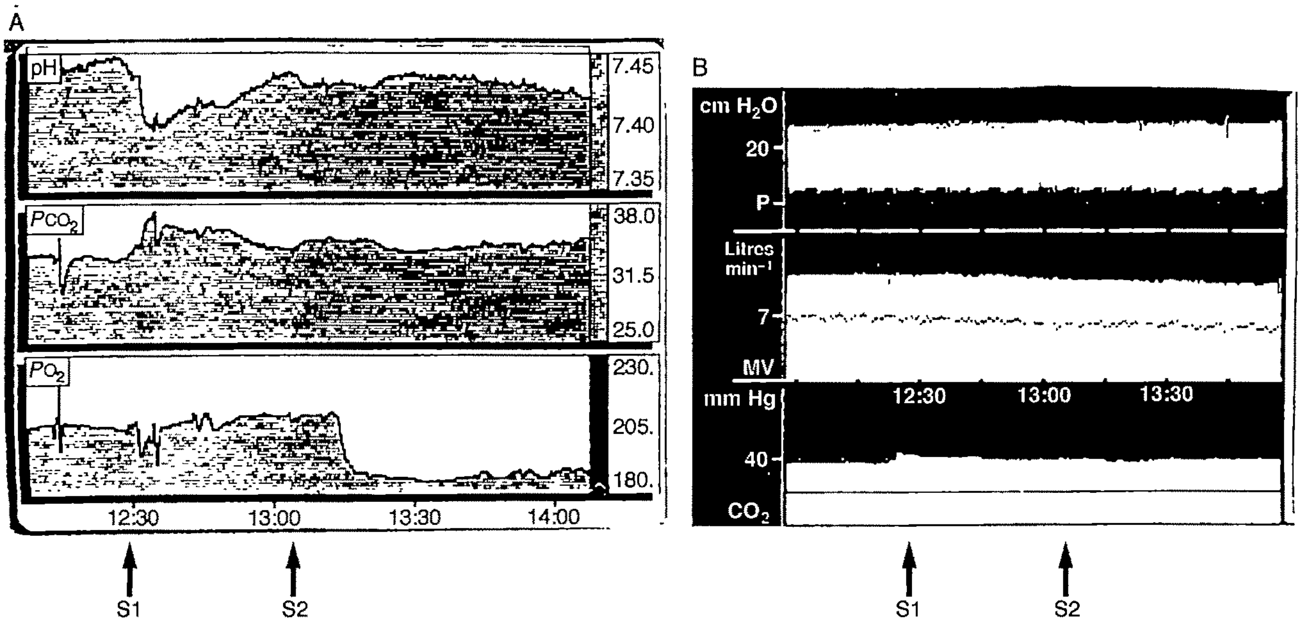

Fig 3 (A) Trend display of arterial blood gas analyses recorded by Paratrend 7 and (B) capnogram recorded by Ultima in case 3. A slight increase in Pa_{CO_2} and decreases in pH and Pa_{O_2} were observed at S1, but not at S2.

Figure 1). Paraspinal muscle contraction was not observed and there were no changes in any of the physiological parameters measured (Figure 1).

Case 2

A 14-yr-old girl weighing 37 kg with no history of neuromuscular disease underwent corrective surgery for idiopathic scoliosis. Premedication and induction were the same as in case 1. Anaesthesia was maintained with 65% nitrous oxide in oxygen and 1.5–2.0% sevoflurane and fentanyl 1–2 μg kg^{-1} was given every hour. To evaluate the degree of neuromuscular blockade, we observed the response of the thumb to train-of-four (TOF) stimulation of the right ulnar nerve using mechanomyography. The electrodes used for measuring

SSEPs were placed directly in the epidural space at T1/T2 and L3/L4. Paraspinal muscle contraction appeared at a stimulus intensity of 0.8 mA. Direct epidural stimulation was performed (9 mA, 16 Hz, 0.2 ms) 10 min after administration of vecuronium 0.05 mg kg^{-1}. At this time, only the first twitch of the TOF response was detectable. Slight paraspinal muscle contraction was observed. The Paratrend 7, placed in the radial artery, showed an increase in Pa_{CO_2} and decreases in pH and Pa_{O_2}, and the Ultima showed an increase in end-tidal carbon dioxide concentration (Figure 2, S1). Further measurements of SSEPs were carried out after additional doses of vecuronium (Figure 2, S2 and S3). Only slight changes in the Pa_{CO_2}, pH, Pa_{O_2} and end-tidal carbon dioxide concentration were observed. When the TOF ratio was 100%, measurement of SSEPs was performed again. This measurement was performed without warning the anaesthetists. Marked changes in pH, end-tidal carbon dioxide concentration, Pa_{CO_2} and Pa_{O_2} were observed (Figure 2, S4). The blood lactate concentration also increased, from 0.9 mmol litre^{-1} before epidural stimulation to 8.0 and 12.4 mmol litre^{-1} 10 and 60 min after epidural stimulation, respectively.

Case 3

A 17-yr-old boy weighing 57 kg with no history of neuromuscular disease underwent corrective surgery for idiopathic scoliosis. Premedication, induction and maintenance of anaesthesia were performed as in case 1. To evaluate the degree of neuromuscular blockade, we observed the response of the thumb to TOF stimulation of the right ulnar nerve using mechanomyography. The electrodes used for measuring SSEPs were located directly into the epidural space at T1/T2 and L3/L4. After confirming the occurrence of paraspinal muscle contraction at a stimulus intensity of 0.8 mA, vecuronium 0.1 mg kg^{-1} was given to obtain complete neuromuscular block. Ten minutes after vecuronium administration, only the first twitch of the TOF response was detectable. Slight paraspinal muscle contraction with epidural stimulation (8 mA, 16 Hz, 0.2 ms) was observed. There were slight increases in arterial pressure and heart rate. The Paratrend 7 showed an increase in Pa_{CO_2} and decreases in pH and Pa_{O_2}, and the Ultima showed an increase in end-tidal carbon dioxide concentration (Figure 3, S1). Twenty minutes after stimulation, vecuronium 0.08 mg kg^{-1} was given. Epidural stimulation was performed again when there was no response to TOF stimulation. Paraspinal muscle contraction was not observed. Arterial pressure, heart rate and end-tidal carbon dioxide concentration remained stable. There were no changes in pH, blood gas or end-tidal carbon dioxide concentration (Figure 3, S2).

In all cases, blood samples directly obtained from the radial artery were also analysed using an ABL 300 blood gas analyser. The results were similar to those measured by the Paratrend 7.

Discussion

The aim of scoliosis surgery is to obtain extensive correction of the spinal curvature without damaging the spinal cord. Measurement of SSEPs has often been used for intra-operative assessment of spinal cord function.[1–3] An alternative method is the wake-up test, which provides only a qualitative assessment of motor function.[9] For the latter test, anaesthesia should be adjusted, allowing the patient to move his or her feet according to command. SSEPs reflect somatosensory but not motor function of the spinal cord. To measure SSEPs, the stimulus is gradually increased until minimal twitching of the paraspinal muscle is observed.[10] Usually, summation of the SSEPs is repeated 20–100 times by recurrent stimuli of 0.1–0.2 ms in duration, each at a rate of 10–30 Hz and at five to 10 times the intensity that induces paraspinal muscle contraction or SSEPs.[11] In our patients, after observation of paraspinal muscle contraction at a given stimulus intensity, we applied epidural stimulation at a 10-fold higher intensity, at a rate of 16 Hz and a duration of 0.2 ms and the action potential was recorded.

There have been a few reports of complications arising from measurement of SSEPs using epidural stimulation. Accidental epidural perforation or nerve root injury can occur during insertion of the electrodes into the epidural space. Epidural stimulation can also induce such excessive paraspinal muscle contraction that surgery is prevented.[11] However, to the best of our knowledge, our previous report[8] was the first of epidural stimulation inducing excessive paraspinal muscle contraction and changing the patient's haemodynamic state and acid–base balance.

Intense muscle contraction-induced systemic acidosis with the accumulation of muscle metabolites has been reported after *grand mal* convulsions[12] or after succinylcholine medication.[13 14] Erbguth and colleagues[13] reported an increase in carbon dioxide production 1 and 5 min after succinylcholine-induced muscle fasciculation. They concluded that significantly increased metabolic activity was associated with the muscle fasciculation. Christensen and colleagues[14] also reported that administration of succinylcholine 1 mg kg^{-1} induced systemic muscle fasciculation and increased carbon dioxide production, but these phenomena were abolished when pancuronium 0.01 mg kg^{-1} was injected before succinylcholine and the non-depolarizing agent prevented fasciculation. These results suggest that the muscle fasciculation generated by succinylcholine caused increases in carbon dioxide production.

In our patients, we observed an increase in Pa_{CO_2} and decreases in pH and Pa_{O_2} immediately after muscle contraction. In case 1 and 2, lactate concentrations rose 15- to 20-fold 1 h after stimulation. These changes after the measurement of SSEPs were prevented by administration of sufficient vecuronium to produce complete neuromuscular block. These results indicate that excessive muscle contraction induced by direct epidural stimulation increases oxygen demand to a level exceeding oxygen supply and consequently causes lactic acidosis.

Orriger and colleagues[12] studied the time course of lactic acidosis after a single *grand mal* seizure. Their results indicated that metabolic acidosis was a primary result of the seizure, not a secondary result of respiratory or renal acidosis.

The TOF ratio is often used to evaluate the degree of neuromuscular blockade. When only the first twitch of the TOF response is detected, the degree of neuromuscular block is approximately 90–95% and surgery can normally be performed.[15] In these circumstances, epidural stimulation in cases 2 and 3 of the present study caused sufficient muscle contraction to result in slight changes in haemodynamics and acid–base balance. On the other hand, after no response to TOF stimulation in case 3, paraspinal muscle contraction, acidosis and haemodynamic changes were not observed. These observations indicated that complete neuromuscular block is necessary to abolish the adverse effects of epidural stimulation-induced paraspinal muscle contraction.

We used the Paratrend 7 in addition to arterial blood gas analysis using an ABL 300 analyser. The values obtained from the Paratrend 7 have been reported to correlate with arterial values.[16] The Paratrend 7 was therefore thought to be effective in the detection of a change in arterial blood gases in acute acidosis.

In conclusion, direct epidural stimulation to measure SSEPs induces excessive paraspinal muscle contraction and severe metabolic and respiratory acidosis. However, these changes can be prevented by administration of sufficient vecuronium to prevent a response to TOF stimulation. We recommend that SSEPs should be measured after confirmation of complete neuromuscular blockade.

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British Journal of Anaesthesia **86** (**4**): 594–602 (2001)

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Phaeochromocytoma—recent progress in its management

Editor—The review article on phaeochromocytoma by Professor Prys-Roberts was his usual tour de force, but it also raised a number of contentious issues.[1] The stance taken on phenoxybenzamine, an agent that many people with wide experience of these tumours find useful, is at variance with much of the published literature and experience. The argument that the α_2-adrenergic blockade produced by non-selective adrenoceptor antagonists may diminish the negative feedback control normally provided by the activation of these receptors, is unsubstantiated. While this negative feedback is well established in normal individuals, Bravo comments that α_2-adrenoceptor stimulation has no effect on catecholamine release in individuals with phaeochromocytoma.[2] This fact is the basis of the clonidine suppression test, which is designed to distinguish hypertensive patients with high catecholamine levels from those with phaeochromocytomas. In the former, clonidine causes a reduction in circulating catecholamine concentrations, whereas in patients with phaeochromocytoma, no reduction is seen.

The validity and value of this test have been documented.[3 4] The non-competitive nature of the block, labelled by Prys-Roberts as a disadvantage, is precisely the reason why those of us who have favourable experiences with the agent find it useful. In phaeochromocytoma, where the pathology may involve episodic release of vast quantities of catecholamines, non-competitive blockade is an attractive option as the blockade will remain effective regardless of the concentration of circulating catecholamines. Competitive antagonists, on the other hand, are likely to fail in the presence of a sudden surge in catecholamine concentration. Competitive antagonists (phentolamine and doxazosin) have been ineffective in controlling hypertension in three cases of actute phaeochromocytoma in our hospital, whereas phenoxybenzamine has subsequently provided good control.

The suggestion that phenoxybenzamine causes somnolence related to α_2-adrenoceptor blockade is surprising. Whilst the use of alpha adrenergic blocking drugs, particularly phenoxybenzamine, is associated with sedation and fatigue, it is not at all clear that this is due to blockade of the α_2-receptor. Sedation is associated with α_2-stimulation, rather than blockade. My experience with phenoxybenzamine, prazosin and doxazosin suggests that some degree of tiredness during the pre-operative preparation phase of phaeochromocytoma occurs in most patients, regardless of the agent used.

The comments regarding hypotension after tumour excision in patients treated with phenoxybenzamine are perturbing. In their book on phaeochromocytoma, Manger and Gifford[5] comment, 'post-operative infusion of pressor agents is rarely necessary'. They further comment that hypotension associated with phenoxybenzamine 'should not present a major problem, since it can almost invariably be prevented or adequately treated by volume replacement pre-operatively or intra-operatively'.[5]My own experience of over 40 phaeochromocytomas managed with phenoxybenzamine is that hypotension is never a clinical problem, provided that appropriate fluid therapy with crystalloids, colloids and, where necessary, blood, is maintained. This experience is in agreement with that of Manger and Gifford that post-operative hypotension in the face of adequate volume replacement is rare and, when it occurs, strongly suggests blood loss.[5] Excessive oedema is not an observation reported commonly in other reviews of the subject, nor have I seen it. The question must be asked as to whether or not the hypotension and oedema referred to by Prys-Roberts is not a consequence of his particular personal preferences in anaesthetic management. I do not use epidural anaesthesia, as I think it may add to the problems of fluid balance management once the tumour is out and will not contribute to the control of catecholamine release, since this is the consequence of tumour handling rather than adrenergic stimulation. I have also found the relatively slow onset (2–3 min) and offset (15–20 min) of action of phentolamine make it a more difficult agent to use than either nitroprusside or magnesium sulphate. Perhaps the reason for the reported incidence of post-operative hypotension and oedema has as much to do with the entire anaesthetic technique, as with phenoxybenzamine alone.

Prys-Roberts suggests that the use of magnesium sulphate for haemodynamic control in phaeochromocytoma anaesthesia is based on the inhibition of the release of catecholamines from the adrenal medulla by magnesium ions.[1] Magnesium has a wide range of pharmacological effects that have been extensively reviewed recently.[6] The theoretical background to the use of magnesium in the anaesthetic management of phaeochromocytoma has been addressed by O'Riordan in her recent publication.[7] She listed the mechanisms of action of magnesium sulphate as follows: inhibition of release of catecholamines from the adrenal medulla; inhibition of release from peripheral adrenergic nerve endings; direct blockade of catecholamine receptors; vasodilatation by direct effect on vessel walls; antiarrhythmic actions, particularly in the presence of high catecholamine levels; and myocardial protection. The adrenergic blocking effect, vasodilatation and antiarrhythmic actions are the most important in this context.

It has been demonstrated in intact laboratory animals that magnesium sulphate provides excellent adrenergic antagonism in the face of high-dose epinephrine infusions,[8] an effect at least equivalent to that of phentolamine under similar experimental conditions. Magnesium is a potent antiarrhythmic,[9] especially in the face of elevated catecholamine concentrations,[10 11] whereas phentolamine may be associated with cardiac dysrrhythmias and angina.[12] The onset of the effects of magnesium is faster than that of phentolamine and the duration of effect is shorter. In addition, there is a direct magnesium antagonist immediately available in the form of calcium salts. The use of magnesium sulphate is thus soundly based on laboratory evidence supported by extensive clinical experience with my own series, now extending beyond 60 cases, supported by several other reports.[13–17] Clearly, as Prys-Roberts points out, a properly controlled clinical trial between various forms of therapy is unlikely ever to be undertaken. Whether or not the use of magnesium is superior to other forms of adrenergic control remains open to debate, but the experimental and clinical evidence are such as to make it a 'rational technique based on sound pharmacological principles'.

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1 Prys-Roberts C. Phaeochromocytoma—recent progress in its management. *Br J Anaesth* 2000; **85**: 44–57

2 Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RWJ. Clonidine-suppression test: a useful aid in the diagnosis of phaeochromocytoma. *N Engl J Med* 1981; **305**: 623–6

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Editor—Thank you for the opportunity to respond to James's letter. Based on his wide experience of managing patients with phaeochromocytoma, he raises a number of issues each of which requires a response.

I do not dispute the validity of the clonidine suppression test, nor do I question the comments of Bravo and colleagues[1] concerning the mechanism by which it works. However, the clonidine suppression test is normally applied as a diagnostic procedure before the treatment of the patient with phenoxybenzamine. It is well established that non-selective α-adrenoceptor antagonists (phentolamine, phenoxybenzamine) cause a tachycardia as a result of β-adrenoceptor stimulation by circulating norepinephrine, or norepinephrine released at cardiac nerve endings, and that this is related to blockade of pre-synaptic α_2-receptors.[2]

In my review I sought to present a balanced view on the advantages and disadvantages of a non-selective, non-competitive α-antagonist (phenoxybenzamine) *versus* a highly selective, competitive α_1 antagonist (doxazosin). Over the past 12 yr I conducted a sequential trial of phenoxybenzamine (eight patients) and doxazosin (18 patients) all having open surgery for phaeochromocytoma or paraganglionoma, and the evidence for preferring doxazosin is contained in an original article awaiting publication. (Prys-Robert C, Farndon JR. Doxazosin *versus* phenoxybenzamine in the peri-operative management of α-adrenoceptor blockade in patients with phaeochromocytoma. Submitted to *Br J Surg*). Since 83% of the patients receiving doxazosin were predominantly norepinephrine secretors, with normal or sub-normal epinephrine secretion, the use of a selective α_1-adrenoceptor antagonist was rational and, indeed, entirely successful. Post-operative positive fluid balance was significantly lower in patients receiving doxazosin compared to those receiving phenoxybenzamine, and clinically detectable post-operative oedema only occurred in patients treated with phenoxybenzamine. Since the conclusion of that trial a further seven patients have been controlled with doxazosin before laparoscopic resection of their unilateral (six) or bilateral phaeochromocytoma. It has not been necessary to add a β-adrenoceptor antagonist except in those cases known to be epinephrine secretors.

James suggests that hypotension in the immediate post-operative period may be due to the epidural block which I used in the described technique. The same technique was used for patients receiving phenoxybenzamine or doxazosin. We found significantly less hypotension in the latter group. In the absence of randomized trials of these two drugs for pre-operative control of blood pressure, readers will have to judge for themselves which drug is the better. Such trials would be very difficult to mount, not only because of the rarity of phaeochromocytoma, but also because of the diversity of its presentation and behaviour. I stand by my advocacy for doxazosin in view of the unqualified success that Farndon and I have obtained in treating patients for up to 6 months before surgery.[3] We have not had to resort to phenoxybenzamine in any of the last 25 patients.

James has a wealth of experience in using magnesium sulphate for the intra-operative control of cardiovascular responses in these patients. I avoided the use of magnesium sulphate in the patients included in my trial only because I did not wish to introduce an additional confounding factor. I and my colleague Dr Andrew McIndoe, who has taken over the care of these patients since I retired, have used magnesium sulphate as part of the intra-operative management in five patients undergoing laparoscopic excision of phaeochromocytoma. I would endorse James's comments about its benefits.

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1 Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RWJ. Clonidine suppression test: a useful aid in the diagnosis of phaeochromocytoma. *N Engl J Med* 1981; **305**: 623–6

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Volatile anaesthetics and the atmosphere: an end to 'scavenging'?

Editor—We read with interest the article entitled 'Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane', as well as the subsequent communication from McCulloch.[2] In neither paper did the authors discuss whether the evacuation of waste anaesthetics into the atmosphere is acceptable or whether we should be developing techniques to minimize it. Langbein and colleagues concluded that the relative contribution to global warming of all volatile anaesthetics is in the order of 0.03% of total global emissions and that the contribution to greenhouse warming potential (GWP-weighted) emissions is small.[1] Presenting only the magnitude of the relative GWP, however, ignores the fundamental issue that this medical waste remains a source of toxic pollution. Some industries have introduced changes to reduce CFC emissions from aerosols, but anaesthetic waste-gas 'scavenging' methodologies have not changed substantially. While newer anaesthetics (Table 3 in Langbein's paper) have less ozone-depleting potential, they still have significant GWP, up to 1900 times the global warming intensity of carbon dioxide.[3]

One new technology, being commercialized by Blue-Zone Technologies Ltd, a Canadian company, may be of special value in this respect. Used under license from Union Carbide, and originally used to reduce industrial CFC emissions (US patents 5,231,980 and 5,515,845 as well a related international patents), this technology uses a proprietary, synthetically manufactured, hydrophobic, organophilic high silica zeolite (Deltazite™[†]) as a molecular sieve absorbent. To our knowledge, however, it has not undergone clinical testing as a 'scavenging' technique for anaesthetic waste emissions. The important potential value of using this scavenging technology is that it would potentially permit the reclamation of the volatile anaesthetic compounds.

We recently conducted a preliminary feasibility study that showed that approximately 750 g of Deltazite™ totally removes 1% exhaled isoflurane from a scavenging system for up to 8 h. No isoflurane was detected exiting the gas recovery canister until 8 h after the study began, when 'breakthrough' occurred. Clinical studies are obviously required to fully evaluate this technology; however, the ability to avoid completely the emission of halogenated anaesthetic vapours into the atmosphere may be a future possibility.

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Conflict of Interest

Although the authors are not paid consultants to Blue-Zone Technologies Ltd, the company has agreed to donate a percentage of profits to a Department of Anaesthesia Research Fund at the University of Toronto, where the authors hold academic appointments.

1 Langbein T, Sonntag H, Trapp D, Hoffmann A, Malms W, Roth E-P, Mors V, Zellner R. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth* 1999; **82**: 66–73
2 McCulloch A. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth* 2000; **84**: 534–6
3 IPCC (Intergovernmental Panel on Climate Change), United Nations, IPCC WGI Third Assessment Report, Expert Review, Table 6.8, April 2000.

Editor—Byrick and Doyle raise an interesting point that was outside of the scope of Langbein and colleagues' paper[1] and my response[2]: whether or not to scavenge exhaled anaesthetic. On first acquaintance it would seem commendable to remove the anaesthetic residue. The most important consideration must be hygiene in the workplace and the exhaled gases must be disposed of in such a way as to be harmless to the other occupants of the building. If the gases are delivered into the atmosphere, sufficiently dilute to avoid being toxic pollution and sufficiently remotely, the anaesthetic traces are rendered harmless by natural oxidation. In the case of isoflurane this process takes place with an atmospheric lifetime of 3.2 yr. The resulting small accumulation of isoflurane in the atmosphere gives it a Global Warming Potential (GWP) in the region of 350 kg of CO_2 equivalent per kg released; much less than the number implied by Byrick and Doyle for this sort of compound. Furthermore, in my previous response, I showed that Langbein had seriously overstated the total contribution of volatile anaesthetics to global warming.

None of this, however, helps to judge whether or not scavenging makes good environmental sense. To put that sort of decision into context it is worth noting that the recovered isoflurane in the test quoted by Byrick and Doyle would have had the same global warming impact as the air exhaled by the treated patients over just 3 days. Such a tiny contribution, alone, does not justify the difficulty and danger of concentrating a cocktail of exhaled anaesthetics onto a solid substrate. In my view, this material could not be recovered for safe re-use and, because the agents are concentrated, would be classified as hazardous waste, disposal of which could be more damaging to the environment than simple release into the atmosphere.

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1 Langbein T, Sonntag H, Trapp D, Hoffmann A, Malms W, Roth E-P, Mors V, Zellner R. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth* 1999; **82**: 66–73
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Hypoxaemia, platypnoea, orthodeoxia and right-to-left shunts

Editor—May I congratulate Marples and colleagues on their interesting case series describing acute right-to-left inter-atrial shunt (RLIAS).[1] They correctly describe a strong association between the unusual sign of platypnoea and RLIAS, and suggest that the combination of unexplained acute hypoxia in a patient with platypnoea and/or orthodeoxia should raise the possibility of RLIAS and be investigated with bubble contrast echocardiography.

Another unusual condition involving right-to-left shunting, whilst usually chronic, can present in a very similar fashion with hypoxaemia, platypnoea, orthodeoxia and a positive bubble contrast echocardiograph. Hepatopulmonary syndrome (HPS) is a vascular complication of chronic liver disease.[2] It is characterized by the triad of liver disease, arterial hypoxaemia, and intrapulmonary vascular dilatation. The hypoxaemia is usually multifactorial in aetiology, with (to varying degrees) ventilation–perfusion mismatch, oxygen diffusion limitation and true intrapulmonary shunts all playing a part. Whilst the hypoxaemia associated with HPS usually responds to increased inspired oxygen concentrations, the proliferation of intrapulmonary vascular dilatations in the basal regions of the lung account for the common associated signs of platypnoea and orthodeoxia.

As with RLIAS, HPS is best investigated with bubble contrast echocardiography. The presence of microbubbles in the left atrium confirms a right-to-left shunt, but the timing of the appearance of these microbubbles is crucial. If the bubbles appear within two to three cardiac cycles, then the shunt must be intra-cardiac. In HPS however, the microbubbles appear later, typically five to 10 cardiac cycles after injection, confirming passage through abnormally dilated lung vasculature.

[†] Deltazite™ is a trademark of Blue-Zone Technologies, Ltd.

HPS does not always present to hepatologists, as the liver disease may be occult, and hypoxaemia may be the overriding feature. There is some evidence that HPS is reversible with liver transplantation, and that debilitating hypoxaemia secondary to HPS should be referred to a transplant centre for consideration, even if the underlying liver disease is not end-stage.

The combination of unexplained hypoxia in a patient with platypnoea and/or orthodeoxia should be investigated with the diagnoses of RLIAS and HPS in mind.

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1 Marples IL, Heap MJ, Suvarna SK, Mills GH. Acute right-to-left inter-atrial shunt; an important cause of profound hypoxia. *Br J Anaesth* 2000; **85**: 921–5
2 Isaac J, Manji M. The hepatopulmonary syndrome. *Curr Anaesth Crit Care* 1997; **8**: 237–40

Editor—We were interested to read the case reports on acute right-to-left inter-atrial shunts (RLIAS) by Marples and colleagues[1] and we would like to highlight another cause of this complication. Acute RLIAS is a well-recognized complication occurring immediately following the placement of left ventricular assist devices (LVAD), a procedure not uncommonly performed at our institution.

The activation of the LVAD causes the left side of the heart to collapse as most of the blood entering the left ventricle is 'sucked' into the LVAD inflow pipe. This results in an acute fall in left atrial pressure and consequently, in the presence of a patent foramen ovale (PFO), in acute right-to-left shunting of blood. Members of our surgical department estimate that this complication occurs in approximately five percent of cases (personal communication, C. Bowles, M. Yacoub).

The American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force[2] have published guidelines on the indications for transoesophageal echocardiography (TOE) and list LVAD insertion to be in category II (supported by weaker evidence and expert consensus).

We and others[3] have found TOE during placement of LVADs to be very useful; not only for the diagnosis of PFO but for other well documented indications which may justify including this indication within the ASA/SCA category I group (supported by the strongest evidence or expert opinion.

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1 Marples IL, Heap MJ, Suvarna SK, Mills GH. Acute right-to-left inter-atrial shunt; an important cause of profound hypoxia. *Br J Anaesth* 2000; **85**: 921–5
2 Practice guidelines for perioperative transesophageal echocardiography. A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology* 1996; **84**: 986–1006
3 Mets B. Anesthesia for Left Ventricular Assist Device Placement. *J Cardiothorac Vasc Anaesth* 2000; **14**: 316–26

Editor—Thank you for the opportunity to respond to the interesting comments made by Dr Isaac. He discusses hepatopulmonary syndrome (HPS) as a cause of non-cardiac right-to-left shunt, which may present in a similar fashion to right-to-left inter-atrial shunt (RLIAS). His observations support the message that right-to-left shunt should be considered in patients with unexplained hypoxia, particularly those with platypnoea/orthodeoxia. The role of bubble contrast echocardiography in the investigation of right-to-left shunt is further supported because the number of cycles at which bubbles appear will distinguish RLIAS from HPS.

Smith and Mitchell present an unusual cause of RLIAS. The placement of ventricular assist devices is highly specialized but is an indication to search for a patent foramen ovale by echocardiography in the pre-operative period. This example illustrates that altered haemodynamics and distortion of normal cardiac anatomy can result in RLIAS.

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Acute right-to-left inter-atrial shunt

Editor—I was interested to read the report by Marples and colleagues of three patients with acute right-to-left inter-atrial shunt.[1] They recommend the use of bubble contrast echocardiography for its detection.

An alternative method would be to use a transpulmonary indicator, such as is used for cardiac output measurement by indicator dilution. Figure 1 shows arterial plasma lithium concentration recorded following injection of lithium chloride 0.3 mmol via a central venous catheter for measurement of cardiac output at the start of an operation for aortic and mitral valve replacements. The resulting curve was unexpected, with the initial

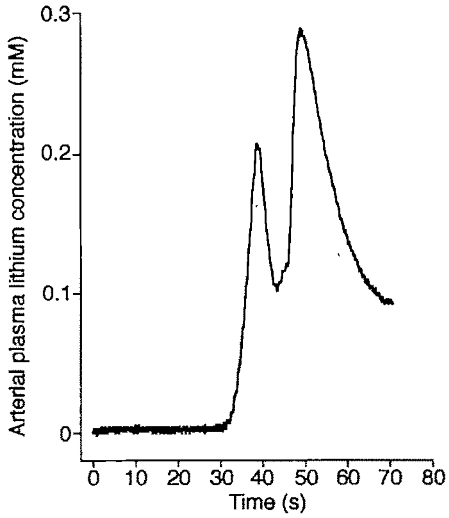

Fig 1.

peak being caused by the indicator passing from right to left through a patent foramen ovale which had been diagnosed preoperatively by transoesophageal echocardiography. It is not possible to derive cardiac output from this curve or to quantify the shunt, since the indicator is not completely mixed with the blood in the right atrium and therefore the amount of lithium chloride passing through the shunt is not necessarily in proportion to the flow through it.

We have previously reported an unsuspected right-to-left shunt through a patent foramen ovale in a 5-day-old infant.[2] In that case the reversal of the shunt was secondary to pneumonia and the distortion of the lithium dilution curve was more subtle.

We should probably be more careful to exclude air bubbles from intravenous infusions.

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Conflict of Interest

R.A.F. Linton is a consultant to LiDCO Ltd.

1 Marples IL, Heap MJ, Suvarna SK, Mills GH. Acute right-to-left interatrial shunt; an important cause of profound hypoxia. *Br J Anaesth* 2000; **85**: 921–5

2 Linton RA, Jonas MM, Tibby SM, *et al.* Cardiac output measured by lithium dilution and transpulmonary thermodilution in patients in a paediatric intensive care unit. *Int Care Med* 2000; **26**: 1507–11

Peripheral nerve stimulation end-point for thoracic paravertebral block

Editor—Thank you for the article by Pusch and colleagues[1] describing the sonographic measurement of needle insertion depth in paravertebral block for breast surgery. Their technique should improve safety and confidence particularly when teaching the method. However, even with careful attention to surface landmarks and with the advantage of these sonographic indices, it is still possible for the initial insertion of a block needle to miss the intended first contact with a thoracic transverse process and risk pneumothorax. We have therefore adapted our technique to include a peripheral nerve stimulation (pns) end-point to signify entry into the paravertebral space and guard against pleural puncture. On all occasions to date when we have accidentally missed initial contact with a transverse process we have been saved from entering the pleura by the sentinel twitch of the intercostal muscles.

Before breast surgery performed either under regional anaesthesia alone, or for post-operative pain relief after general anaesthetic, our practice is to turn the patient laterally (operation side up) and identify surface markings for the tips of the transverse processes pertaining to the distribution of the surgical wound. We use an electrically insulated 23 g 70 mm local anaesthetic needle charged by a constant-current Polystim generator. The equipment is preset to deliver 1 mA at 1 Hz prior to piercing the skin. The ground silver chloride electrode is placed on the anterolateral chest wall. The needle is walked off the caudal edge of the appropriate transverse process and advanced slowly. The lateral chest wall is palpated firmly by a flat hand. When the appropriate intercostal muscles twitch strongly (at a needle depth of about 1 cm deep to the transverse process) we stop advancing the needles and reduce the current to 0.4 mA, at which point the muscle twitch decreases or ceases. The needle is then advanced very slowly, usually less than a further 5 mm, until the muscles again twitch strongly. We interpret this as an end-point for the paravertebral space. Often the end-point twitch is lost on injection of local anaesthetic. Interestingly, the erector spinae muscles only twitch strongly when the needle placement is too medial possibly signifying stimulation of the posterior primary rami.

An alternative is to electrically adapt an intravenous cannula in a manner similar to that reported by Ben-David, Lee and Croitoru.[2] We use a 20-gauge needle inserted into an 18-gauge Venflon cannula to which the above protocol is applied. Alternatively a 22-gauge Quincke spinal needle (non-insulated) can be electrically adapted by application of an alligator clip to the shaft but in this case we start with the generator set at the much higher setting of 5 mA and then reduce it down to 2 mA.

The sonographic measurements described by Pusch and colleagues[1] are welcome as they will enable us to confirm that the depth of our pns end-point lies between the transverse process and the pleura. We are presently comparing the use of this pns end-point with the classic loss of resistance technique for paravertebral block by a randomized controlloed trial.

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1 Pusch F, Wilding E, Klimscha W, Weinstabl C. Sonographic measurement of needle insertion depth in paravertebral blocks in women. *Br J Anaesth* 2000; **85**: 841–3

2 Ben-David B, Lee E, Poitoru M. Psoas block in surgical repair of hip fracture: a case report and description of a catheter technique. *Anesth Analg* 1990; **71**: 298–301

Editor—Thank you for allowing me to respond to Dr Wheeler's letter. He describes an interesting technique to increase the safety of paravertebral block. Loss of resistance perceptible during puncture of the paravertebral space is different from that experienced on identifying the epidural space because the resistance to injection of saline or air is higher. It therefore needs experience to detect reliably paravertebral puncture according to the level of the thoracic vertebrae. In addition, needle direction needs to be varied after contacting the transverse process. As one works down the thoracic vertebrae, an increasing distance for needle insertion from the anatomical midline is necessary. All these factors require experience to increase the safety and feasibility of paravertebral block. Applicable teaching methods need to be identified to increase the popularity of this technique.

Contrary to the statement of Wheeler, in experienced hands it is usually not difficult to contact the transverse process, but if difficulty is encountered ultrasound is useful. Wheeler mentioned too medial a needle placement. In my opinion, with regard to the anatomy of the parietal pleura and the paravertebral space, too medial a puncture reduces the risk of pleural puncture. Due to the bony structures, sonographic guidance requires a slightly greater distance from the midline for needle insertion tip compared to the loss of resistance technique so that the tip of the needle can be reliably visualized during puncture. Our sonographic method can be improved by adjusting the position of the needle, and the position of the scanning head, both of which improve the visualization of the test dose injection.

Even injection of small increments of local anaesthetic into the paravertebral space causes discomfort for a few seconds. We always inform the patient about this side-effect before the injection. I think, therefore that peripheral nerve stimulation for paravertebral block using the high voltage described in this letter, must increase discomfort for the conscious patient and reduce the acceptability of paravertebral block. In my opinion Wheeler's technique could be improved and may then represent a useful teaching method.

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Use of intravenous opioids to reduce airway irritation during induction of anaesthesia with desflurane

Editor—We read with interest the paper by Kong and colleagues[1] reporting the use of intravenous opioids to reduce airway irritation during induction of anaesthesia with desflurane. As the goal of research in anaesthesia is to make us more effective anaesthetists, clinically orientated studies such as theirs are welcome. However, we have some concerns about the study and would be grateful for the authors' comments.

First, the authors state in their introduction that desflurane gives 'rapid induction and emergence from anaesthesia', but this statement is not supported by the study of Yasuda and colleagues[2] which they quote. Here, subjects breathed a steady 2% inspired desflurane concentration when they were already anaesthetized. Thus their study merely documents a more rapid approximation of F_A and F_I for desflurane compared to isoflurane. It does not demonstrate more rapid induction of anaesthesia with desflurane. Thus this reference actually supports the earlier statement 'desflurane is a halogenated ether with low solubility'.

It is undoubtedly true that desflurane is less soluble than other volatile anaesthetic agents, but this in itself does not confer rapidity of action. We suggest that this might be more realistically phrased: 'Desflurane *might be predicted to produce* rapid induction and emergence from anaesthesia'. To expect drugs to behave according to pharmacological principles when used in clinical practice is to court disappointment. As our day-to-day experiences with patients in intensive care and chronic pain have taught us, a drug's effect may be quite different from that predicted from our theoretical knowledge of its actions.

Second, we were puzzled by the authors' findings relating to induction times and expired concentration (Table 2). Averages are expressed both as means and medians, but it is not clear what statistical distribution is assumed for these data, nor which tests were applied to establish significance. Assuming these results are valid, the expired desflurane concentrations are actually higher in the patients who were given morphine, whereas one might expect them to be lower, as opioids should reduce the MAC of desflurane required for a particular level of anaesthesia. When this is mentioned in the discussion, the authors suggest that it is morphine-induced sedation which leads to the difference. If patients are sedated, one would expect a lower expired desflurane concentration to be needed to produce loss of response to command. On the other hand, it can be postulated that, if morphine induces respiratory depression, uptake of desflurane into pulmonary capillary blood is slower, and brain concentration will lag behind expired. This does not seem to be borne out in the study's results, as the incidence of apnoea was in fact significantly lower in the morphine group, suggesting that respiratory depression was not a problem. We would be interested in the authors' further thoughts on this point.

Third, there was no evidence of a difference between the three groups in the time to loss of response to command (though the authors refer to this, somewhat optimistically, as 'time to induction'). The authors may well be correct in their interpretation that the long time (typically 5 min) to loss of response was due to the slow increase of desflurane concentration. It could also be that the study numbers were too small to show a difference, and we wonder if a power calculation was performed whilst the study was being designed. It would have been quite correct to base this on the expected difference in incidence of adverse events, as these were the outcomes of interest of the study, but in that case one must be cautious about drawing conclusions about incidental outcomes such as time to loss of response.

Finally, the authors' conclusion that 'pre-treatment with morphine or fentanyl reduce the incidence of airway irritation to a value similar to that reported with sevoflurane' is supported by their findings but ignores the fact that induction of anaesthesia (as opposed to simply rendering the patient unresponsive to command) with sevoflurane is quicker and simpler. We suspect that no pharmacological manipulation can make desflurane's clinical performance live up to its enthusiasts' theoretical predictions.

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1 Kong CF, Chew STH, Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85**: 364–7

2 Yasuda N, Lockhart SH, Eger EI, Weiskopf RB, Johnson BH, Freire BA *et al.* Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology* 1991; **74**: 489–8

Editor—Thank you for the opportunity to reply to the four points raised by Smith and Rauf regarding our paper.[1] First, they dispute the fact that desflurane gives 'rapid induction and emergence from anaesthesia'. Wrigley and colleagues[2] compared gaseous desflurane with intravenous propofol induction in four groups of patients. They found that desflurane caused rapid loss of consciousness in approximately 2 min and that induction-incision times were comparable between inhalational and intravenous induction. Nathanson and colleagues[3] report more rapid emergence and shorter time to extubation with desflurane compared to sevoflurane following outpatient surgery. In the case of the inhalational agents, pharmacokinetic and pharmacodynamic data can be used in computer-assisted modelling,[4] to simulate the clinical situation with a high degree of agreement.[5]

Second, as the data was non-parametric, we used Kruskal-Wallis test to analyse the variance between the three groups. We do not know the explanation for the higher expired desflurane concentration in our morphine group. Intravenous morphine produces a reduction in respiratory rate with an inadequate compensatory increase in tidal volume. This could have led to a slower uptake of desflurane causing the brain concentration to lag behind as suggested. Incidentally, an alternative or additional explanation to the effect of opioids in reducing the incidence of airway irritability, may lie in their ability to suppress coughing.[6]

Concerning the third point, a power calculation was done whilst the study was being designed. Based on our pilot study, the incidence of coughing was 30%; assuming α of 0.05 and power of 0.8, the sample size required is 43 per group. We decided arbitrarily to round up the number to 60 in each group.

Finally, we do not suggest that desflurane induction is a substitute for sevoflurane in every situation. The use of narcotics reduces the incidence of airway irritation, to the extent that desflurane induction can be considered, in order to exploit its lower solubility where indicated.

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1 Kong CF, Chew STH, Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85**: 364–7
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6 Kong CF, Chew STH, Ip-Yam PC. The anti-tussive effect of narcotics reduces the incidence of airway irritability during desflurane induction in adults. *Anesthesiology* 1999; **91**: A431

Overdose of ketoprofen could be dangerous

Editor—I was interested to read the article by Kokki and colleagues.[1] In their study the authors included patients between the age of 1–9 y and thus the patients varied considerably in body weight. However, these workers chose to use an initial dose of ketoprofen 25 mg for all patients, irrespective of body weight. They also gave ketoprofen 1 mg kg^{-1} within 5 h of the last dose before discharge from hospital.

Ketoprofen is not recommended for use in children.[3] The maximum recommended dose for an adult is 200 mg in 24 h and it has to be given in 2–4 divided doses. This is equivalent to 2–3 mg kg^{-1} day^{-1}. The authors[1] used a drug that is not recommended for children and some of their patients must have received an overdose in such a short period of time. Although they notified the National Agency for Medicines about their use of ketoprofen in children weighing less than 20 kg, they probably did not notify the actual dose used. It would have been more appropriate to use this drug on the basis of body weight, which is standard medical practice.

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1 Kokki H, Tuomilehto H, Tuovinen K. Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous route. *Br J Anaesth* 2000; **85**: 836–40
2 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. London: BMA, RPS, 2000. (No. 39)

Editor—We appreciate Dr Mandal's comments about our manuscript.[1] The letter raised an important issue of the dosing of ketoprofen in children. Maunuksela has recommended an initial dose of ketoprofen 2.5 mg kg^{-1}[1,2] As most of the patients in our study were over 10 kg, only a few patients in the ketoprofen groups received the maximum dose. However, we have shown that ketoprofen is an effective analgesic in much lower doses[3,4] and in a recent study doses as small as ketoprofen 0.3 mg kg^{-1} performed significantly better than placebo.[5] We believe that in the present study all children in the ketoprofen groups received an analgesic dose of drug; this was proven by our result.

The short half-life of ketoprofen, 2 h[6], allows frequent dosing in acute pain management. This is an advantage as a second dose can, when necessary, be administered soon after the first. Pain is a common problem even after minor surgery in children[7,8] and therefore a proactive approach is recommended.[9] In day case surgery, our practice is to give a prophylactic dose of ketoprofen i.v. at discharge.

We have notified the National Agency for Medicines about the dose of ketoprofen used in these children. We agree that it is appropriate to use all drugs in children on the basis of body weight. With suppositories this goal cannot be achieved. We recommend using ketoprofen intravenously as long as possible. Syrup would be used for small children.[6] Because children dislike suppositories[7,8] and we therefore do not commonly use rectal administration in conscious children.

Dr Mandal has provocatively titled this letter 'Overdose of ketoprofen could be dangerous'. However, he does not give any definition of what he means by an overdose. Our results show that ketoprofen 3 mg kg^{-1} as an initial dose is safe in children[5] and that at least 5 mg kg^{-1} can be used over 24 h.[10–13] There is however an urgent need for further studies to refute common fallacies about pain and pain treatment in children.

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1 Kokki H, Tuomilehto H. Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous route. *Br J Anaesth* 1997; **85**: 836–40
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7 Sepponen K, Kokki H, Ahonen R. Training of medical staff positively influences postoperative pain management at home in children. *Pharm World Sci* 1999; **21**: 168–72
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9 Wolf AR. Tears at bedtime: a pitfall of extending paediatric day-case surgery without extending analgesia. *Br J Anaesth* 1999; **82**: 319–20

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12 Kokki H, Nikanne E, Ahonen R. The feasibility of pain treatment at home after adenoidectomy with ketoprofen tablets in small children. *Paediatr Anaesth* 2000; **10**: 531–5

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Extra cranial sources of S100B

Editor—We read with interest the correspondence of Kuzumi and colleagues[1] regarding serum S100 protein as a marker of cerebral damage during cardiac surgery, and the reply from Shaaban Ali and colleagues.[2] While we agree with many of the points raised, we feel that there may be unrecognized problems with the evidence sited for the extra-cranial source of S100B, as well as issues raised in the accompanying editorial to the original article by Jonsson and colleagues.[3]

First there is the problem of nomenclature and what is actually being detected. The S100 proteins have had a number of different classifications which have evolved as knowledge of these proteins has progressed. It is entirely possible to use the term S100β to refer to either the beta-type monomer or the beta-beta homodimer. In the latest classification S100B refers to the beta monomer, and S100BB or $S100B_2$ refers to the beta-beta homodimer.[4] We have recently confirmed with the manufacturer (Byk-Sangtec, Germany) that the antibody used in the commonly used assays for S100B (both LIA-Mat and RIA-Mat versions) is directed against the monomer. Therefore the antibody will pick up the monomer or any dimer which includes the S100B chain. Thus it is entirely possible that S100BB is being released from injured brain and an intra-thoracic source of, for example, S100AB is contaminating the system. We would therefore support studies to determine what form of S100 protein is being released in these patients, for example by detecting the S100A monomer. In future it is our opinion that all studies should state exactly what is being detected to prevent any further confusion of this kind.

The second confounding factor is a matter of pharmacokinetics. By implication the blood salvaged in the cardiotomy suckers is collected in the interval between the last transfusion and the start of the one in question. Therefore, unless there has been further release of S100B, the levels in the blood oozing into the thoracic cavity (and thus the cardiotomy suckers) must be greater than that in the systemic circulation while it is being given back to the patient, and thus acts as a bolus dose. Indeed this principle was used to calculate the elimination rate of S100B in this situation by estimating the total amount in each bolus.[3] Such peaks as are demonstrated may be a consequence of this and not a representation of an extracranial source. Moreover, as coagulation takes place inside the thoracic cavity it is possible that low molecular weight proteins, such as the 11.5 kDa S100B monomer, are selectively exuded through maturing thrombus by virtue of their small molecular size. This would concentrate these proteins in the drained fluid used for autotransfusion, and may in part also account for the high levels observed in the cardiotomy suction.

In an accompanying editorial to the paper by Jonsson and colleagues[3] it is pointed out that auto-transfused blood is a potential source of micro-emboli that could be causing cerebral damage and thus S100B release.[5] These may be removed from the system if auto-transfusion or cell washing is used. Thus the multiple peaks demonstrated could alternatively represent small brain insults from this cause. The rise in systemic levels demonstrated is certainly consistent with that shown in minor traumatic brain injury.[6]

We conclude that without assessing the dose and type of S100 proteins delivered into the thoracic cavity during cardiotomy suction it is extremely difficult to eliminate these confounding factors. The evidence for an extracranial source of S100B in this situation cannot be considered proven without further investigation. We concur with the correspondents and Jonsson and colleagues that one method to eliminate these confounding factors is to avoid auto-transfusion or to use cell washing techniques.

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1 Kuzumi E, Vuylsteke A, Guo X, Menon DK. Serum S100 protein as a marker of cerebral damage during cardiac surgery. *Br J Anaesth* 2000; **85**: 936

2 Shaaban Ali M, Vaughan RS, Harmer M. Serum S100 protein as a marker of cerebral damage during cardiac surgery. *Br J Anaesth* 2000; **85**: 936–7

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The proseal LMA: preliminary data

Editor—The standard LMA[†] has been used in patients in whom tracheal intubation and ventilation through the face mask are difficult or impossible. Although it has been used successfully in elective and emergency patients with a difficult airway, a limiting factor is the lack of airway protection from regurgitated gastric contents.[1]

Brain has designed a new laryngeal mask, the ProSeal LMA (PLMA), incorporating a drainage tube and a dorsal cuff. It provides a channel opening into the upper oesophagus for insertion of standard nasogastric tubes, which should prevent accidental gastric insufflation and permit drainage of gastric fluids. The design incorporates a finger locating strap for the index finger or thumb, which can be used as an introducing tool for ease of insertion.[2]

The PLMA was inserted using the index finger technique in 50 anaesthetized patients, using a size #4 for females or a #5 for males. We evaluated: ease of insertion of the PLMA; the seal; ease of ventilation; fibreoptic visualization of the vocal cords; and the incidence of post-operative complications. Fibreoptic score decoding was: 1=vocal cords not seen; 2=vocal cords plus anterior epiglottis visible; 3=vocal cords plus posterior epiglottis visible, and 4=only vocal cords visible.

[†] LMA® is the property of Intavent Limited.

Insertion of the PLMA was difficult in 13/50 patients and impossible in 4/50. The vocal cords and/or epiglottis were visualized in 47/50 patients. The post-operative complications were: cough 1/50; sore throat 1/50; and pain on swallowing 2/50.

To obtain an effective airway, the device was reinserted in three patients; we had to change the size (#5 rather than #4) in two patients; in three patients we had to pull up the PLMA, and to push it down in four patients. Ventilation was satisfactory in all patients. In those patients whom PLMA insertion was difficult or impossible, the volume of the second cuff was probably an obstacle to proper positioning of the device. The presence of cough or pain on swallowing seems to be related to the size of the PLMA used and to the posterior cuff. Moreover, the post-operative complications following use of the PLMA seem to be similar to those of an LMA.[3–5]

We conclude that the PLMA needs further evaluation of its ease of insertion and its role in airway management in addition to the LMA.

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1 Brimacombe J, Berry A. The incidence of aspiration associated with Laryngeal Mask Airway—A meta-analysis of published literature. *J Clin Anaesth* 1995; **7**: 297–305

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Book Reviews

Day Case Anaesthesia (first edition). Ian Smith (editor). Published by BMJ Publishing Group, London. Pp. 252; indexed; illustrated. Price £30.00. ISBN 0-7279-1422-7.

This book is part of a series entitled *Fundamentals of Anaesthesia and Acute Medicine* published by BMJ Books. It consists of a number of reviews by authors from the UK, Australia, Norway and Sweden. The editor states that, in addition to providing up-to-date and authoritative views, the book is intended as a convenient and practical guide for practitioners starting out in day surgery or trying to set up a day surgical unit. These aims are achieved in a book that is well edited with very little overlap between the chapters. When overlap does occur it serves to emphasize important points. In a practical subject it is very useful to have the authors' views on controversial issues and appropriate anaesthetic techniques. The considerable emphasis on follow-up of day-cases for audit purposes and to allow continued development of practice is also laudable. The use of boxes to summarize important points or useful practical advice works very well. There are one or two errors in the boxes but these are fairly obvious and should not cause confusion. However, the 'overview' at the beginning of each chapter is much less useful because it differs very little from the summary and does not aid in the overall understanding of the subject.

Patient selection, assessment and preparation are dealt with in Chapter 1 in a very practical and commonsense manner. Issues such as patient suitability, need for pre-operative investigations, and information given to patients are discussed. Chapter 2 covers the principles of general anaesthesia including the facilities required in a day unit and techniques for anaesthesia, airway management, fluid therapy, and recovery. However, the author of this chapter has tried to cover too much and consequently some of it is dealt with superficially. For instance, it is recommended that neuromuscular blocking drugs should not usually be reversed without any reference to the potential problems of inadequate reversal.

Inhalation and intravenous anaesthesia in day surgery are reviewed in separate chapters. The agents available, methods of administration and their advantages and disadvantages are detailed. Volatile induction and maintenance of anaesthesia is dealt with in some detail with a comparison of tidal breathing and vital capacity inhaled induction techniques, but there is no mention of the elimination of the danger of anaphylaxis as an advantage of inhalation induction.

There is a comprehensive review of the place of regional anaesthesia in day surgery. Descriptions of several useful techniques are given. However, on page 121, for regional block for inguinal hernia repair, 47 ml of 1% plain lidocaine is recommended. This is more than twice the recommended safe dose.

The principles of the use of sedation for day-cases are well reviewed. There are descriptions of useful techniques and considerable emphasis on the importance of and methods available for careful observation and monitoring of the patient during sedation. Details are given of the pharmacology of available drugs and the use of target controlled infusion, patient controlled sedation and patient-maintained target controlled infusion.

Post-operative pain and emesis are the two problems most likely to lead to unplanned admission after day-case surgery and a chapter is devoted to these topics. Commonsense practical approaches to both subjects are described and include the development of the use of drug combinations for the control of PONV. In a thorough review of assessment of recovery and fitness for discharge there is discussion of future developments in day surgery using hotel beds or extending the hospital stay to overnight so that more extensive surgery can be performed on a day-case basis. However, I do not agree with the unqualified statement that PONV and pain after day-cases could form the basis for comparing anaesthetists. Allowance would need to be made for case-mix and other variables.

The paediatric day-case is the subject of the penultimate chapter reminding the reader that a child is not just a small adult and needs special equipment, facilities, and a different approach from staff. In the final chapter, the editor attempts to predict the future of day surgery and rightly advises great caution regarding the potential development of office-based practice because of the danger of delivering anaesthesia in poorly equipped and supported premises.

This book gives a thorough and up-to-date overview of day-case anaesthesia. It is well written and easy to read with useful tables, illustrations and summaries. Currently, day cases form part of almost all anaesthetists' practice in the UK and day-case surgery will almost certainly continue to expand. Therefore, I would recommend this book as useful CEPD for all anaesthetists. It also provides suitable material for preparation for the Final FRCA examination.

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Drug Effects on Psychomotor Performance, (first edition). Randall C. Baselt. Published by Biomedical Publications, Foster City, California. Pp. 475; indexed. Price US$109. ISBN 0-9626523-4-2.

This book is a comprehensive collection of mini-reviews covering a wide selection of drugs. It represents an overview of 144 drugs in common use today across many categories. A useful Glossary helps identify the different psychometric tests and brings a level of uniformity to the test names. Each review is set out in the same format and is presented alphabetically rather than by category. They start with information on the drug's therapeutic and pharmacological categories, the active metabolites and half-life. For the review itself, the major therapeutic indications are outlined first followed by a chronological list of the published investigations found by the reviewer. Driving studies are listed separately as are the epidemiological studies. Finally, a brief synopsis of the major findings is given in the conclusion.

I found this book very interesting but unfortunately of limited value. What would have been an excellent idea 20 years ago, will have difficulty fitting in to our modern rigorous evidence-based world. The author gives us little information about the inclusion criteria for both the studies and the drugs. For example, why omit the antidepressant Paroxetine? The test battery in the study by Kerr (1992)[1] included Critical Flicker Fusion Choice Reaction Time, Stroop, memory, and visual analogues. Or why not include Wilson and colleagues' study of midazolam as sedation for spinal anaesthesia (using Critical Flicker Fusion, Choice Reaction Time)?[2] Also Michael Trimble summarized the effects of five of these drugs in his book 'Epilepsy, behaviour and cognitive function' but it is not mentioned. As this book is aimed at researchers, clinicians, safety officials, and forensic scientists, I feel that it fails to hit its target audiences.

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One of the main drawbacks of any reference document is its need to be updated. Access to the Internet with its vast, regularly updated, information store is difficult to compete with. Therefore a book like this is out-of-date before it is published (e.g. thioridazine has no mention of cardiac side-effects).

Evidence-based medicine is the watchword of the new millennium and with it comes a specific search rigour (such as in the Cochrane Library and the National Institute of Clinical Excellence (NICE)) for the production of reviews. This gold standard is now the expected format. This book gives us none of the anticipated details of the search strategies used to obtain the studies or why each were included.

Unfortunately, this book also serves to emphasize our differences with America, especially the variances in the issue of drug licenses. For example, the review of clozapine does not mention that it carries a 1–2% risk of fatal cardiac toxicity and that consequently all patients must have regular blood monitoring. Nor does it mention that, despite this problem, it is the drug of choice for resistant schizophrenia. Also bearing in mind minor spelling differences, 32 of the drugs included do not appear in the British National Formulary (BNF): amobarbital, butorphanol, fexofenadine, γ-hydroxybutyrate, hydromorphone, melatonin, meperidine, mepivacaine, methamphetamine, methaqualone, methohexital, methylenedioxymethamphetamine, methylphenidate, mirtazapine, modafinil, nefazone, pentobarbital, phencyclidine, prozepam, propoxyphene, psilocybin, quazepam, secobarbital, sibutromine, tetrahydrocannabinol, tramadol, trihexyphenidyl, valproic acid, venlafaxine, zaleplon, zolmitriptan and zolpidem.

Finally, at the end of each review the author gives a conclusion, presumably a summation of the information given on the findings of the various studies, but we are not given any idea about what data went into making those conclusions. For example, were all the studies included or were some rejected on the methodological quality of the studies?

It is very difficult for the written word to compete in our modern world of high tech, high-speed information. Maybe this book needs to be published as the basis of a web site?

C. Whitehead
Cardiff
UK

1 Kerr JS, Fairweather DB, Mahendran R, Hindmarch I. The effects of Paroxetine, alone and in combination with alcohol, on psychomotor performance and cognitive functioning in the elderly. *Int Clin Psychopharmacol* 1992; **7**: 101–8

2 Trimble M, Reynolds EH, eds. *Epilepsy, Behaviour and Cognitive Function.* Chichester: Wiley, 1987

British Journal of Anaesthesia **86** (**4**): 605 (2001)

Errata

Phaeochromocytoma—recent progress in its management (BJA 2000; 85: 44–57)

The top box in Figure 1 should be labelled 'Neural crest' not 'Neutral crest'.

Malignant hyperthermia: advances in clinical management and diagnosis (BJA 2000; 85: 118–28)

The running heading throughout this article should read 'Malignant hyperthermia' not 'Malignant hypothermia'.

The publisher apologizes for these errors and would like to thank Dr P. Cartwright for pointing them out.

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Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

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2. Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985; 155-79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979

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EDITORIALS

563 Thromboelastography: The Next Step

CARDIOVASCULAR ANESTHESIA
(Society of Cardiovascular Anesthesiologists)

565 Intravascular Volume Replacement and Coagulation
572 TEG® and Major Abdominal Surgery
578 Maximal Activated Clotting Time Versus Celite-Activated Clotting Time
584 Hemodynamic Changes in Aortic Valve Area
590 Acadesine and Reperfusion Lung Injury
596 Predicted Risk of Fatal Heart Failure
602 Inhibition of Ca^{2+} Transients by Morphine
609 Circulating Blood Volume and Hemoglobin-Based Oxygen Carriers
615 Allosteric Modification of Oxygen Delivery by Hemoglobin

AMBULATORY ANESTHESIA
(Society for Ambulatory Anesthesia)

621 Effect of Personality on Midazolam Pharmacokinetics
625 Intraarticular Sufentanil in Knee Arthroscopy
629 Transcutaneous Acupoint Stimulation and Postoperative Nausea and Vomiting

PEDIATRIC ANESTHESIA
(Society for Pediatric Anesthesia)

636 IV Dexamethasone for Adenotonsillectomy
641 Hypertonic Saline and Antidiuretic Hormone in Severe Head Injury
646 Carnitine Palmitoyltransferase I Coma (Case Report)
648 Allergy to Cisatracurium in a Child (Case Report)

ANESTHETIC PHARMACOLOGY
(International Society for Anaesthetic Pharmacology)

650 Sevoflurane in Patients with Renal Failure
656 Determinants of Propofol Induction Dose

TECHNOLOGY, COMPUTING, AND SIMULATION
(Society for Technology in Anesthesia)

662 Monitoring of the Recurrent Laryngeal Nerve During Single-Lung Ventilation (Case Report)

OBSTETRIC ANESTHESIA

665 Spinal Morphine Prolongs Labor Analgesia

NEUROSURGICAL ANESTHESIA

669 Outcome from Head Trauma Plus Hemorrhage

CRITICAL CARE AND TRAUMA

676 Olprinone of Endotoxemia
681 Selective iNOS Inhibition in Septic Rats
688 Paradoxical Fat Embolism (Case Report)
690 Lazarus Syndrome (Case Report)

ECONOMICS AND HEALTH SYSTEMS RESEARCH

693 Cost Per Dose of Succinylcholine
700 Systematic Reviews in Literature

REGIONAL ANESTHESIA AND PAIN MEDICINE

710 Cardiac Output After Spinal Anesthesia
715 Remifentanil Infusion for Severe Postoperative Pain
720 Cervical Block, Ropivacaine vs Bupivacaine
725 Clonidine and Glutamate Antagonists
733 Interaction of Clonidine and Lidocaine
739 Preemptive Dextromethorphan
745 Dexamethasone and Emesis
749 Epidural Anesthesia and Respiratory Distress

GENERAL ARTICLES

755 Diaphragm Motion After Cholecystectomy
762 Colforsin Daropate and Diaphragmatic Fatigue
767 Ethanol and Calcium Sensitivity in Smooth Muscle
775 Hemostasis and Blood Loss After Total Knee Arthroplasty
781 Propofol and Hyperventilation Syndrome (Case Report)
783 Temporomandibular Joint and Difficult Tracheal Intubation (Case Report)
785 Orthopedic Surgery and Factor VIII Inhibitors (Case Report)
787 Evidence-Based Medicine in Anesthesiology (Review Article)
795 LETTERS TO THE EDITOR
798 BOOK AND MULTIMEDIA REVIEWS

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